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MISCELLANEA

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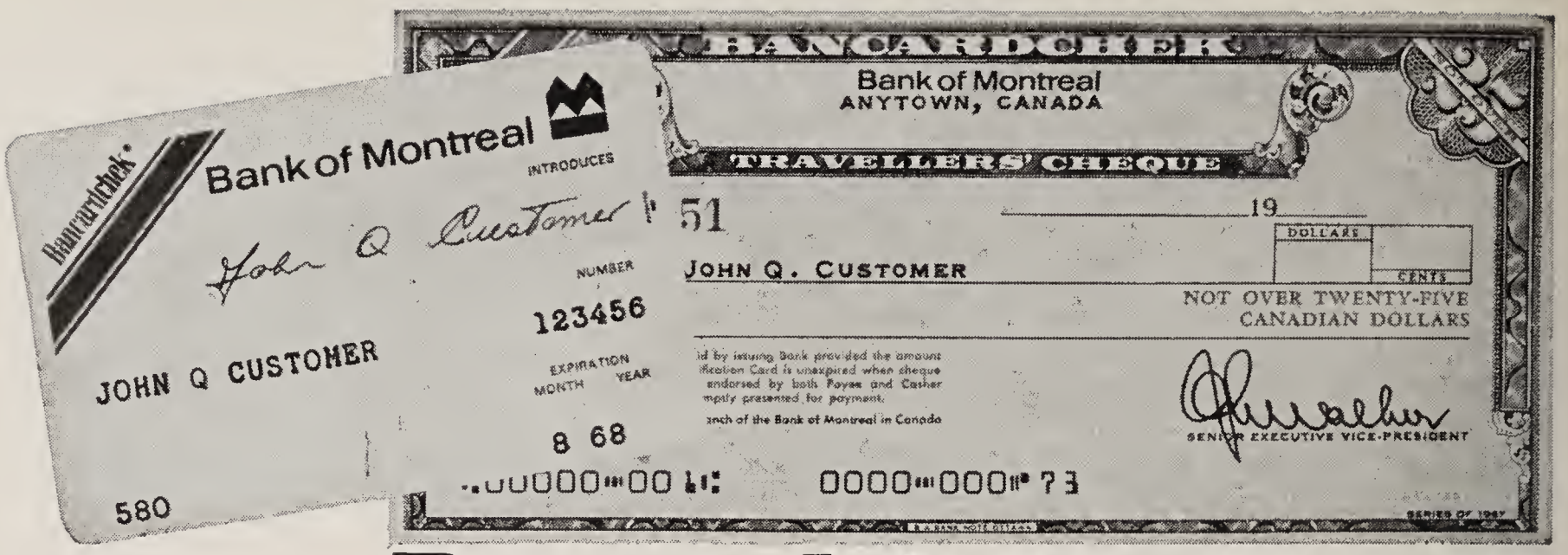

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Guest Editorial

WILLIAM BOYD spent the first ten years of his life in a small fishing village in the North of Scotland. After going to a boarding school in England, he studied medicine at the University of Edinburgh, graduating with J.C.B. Grant in 1908; he received his Diploma in Psychiatry in 1912.

He gradually shifted from Psychiatry to Pathology, and after serving in a Field Ambulance in the early days of the First World War, he was appointed the first full-time Professor of Pathology in the University of Manitoba. It was in Winnipeg that he wrote various books, and introduced a new type of Pathology Museum. In 1937 he became Professor of Pathology in the University of Toronto, and in 1951 he went to Vancouver to take up the position of the first Professor of Pathology in the newly formed Faculty of Medicine of the University of British Columbia, where he remained until the first class graduated in 1954.

Pathology And Disease

The medical student is going to spend the rest of his life combatting disease, either treating it, investigating it, or trying to prevent it. So let us ask ourselves for a moment the simple question: "What is disease?" Very soon we find that the answer is not as simple as the question. The word disease suggests discomfort if not suffering (*dis-ease*), but a person may be diseased without showing any clinical evidence of the fact. The valves of his heart may be thickened, the aorta rough and cracked, and the stomach or lung may be the seat of cancer, and yet the patient has no symptoms; he is not *ill*.

This brings us to the question of pathology, a subject in which I am naturally interested. Pathology has been defined as the study of structure and function in disease, although here again we run into the difficulty of words changing their meaning, for the Greek word *pathos* signifies suffering, which would suggest that all doctors are pathologists, a concept which would certainly not be welcomed by the clinician. So we must revise our definition and say that pathology is the study of disease by the methods of the laboratory. It not only serves as a bridge between the basic sciences of anatomy, physiology and biochemistry on the one hand and medical and surgical treatment on the other; it is essential to an understanding of disease, and without understanding, how can a doctor be expected to treat a disease with success?

Pathology used to be called morbid anatomy, an unfortunate term often used slightingly by the very up-to-date biologist who delves into the problems of disease. But morbid anatomy is not dead and never has been except in the hands of those whose dull minds would take the breath of life from the most vital subject. The world of medicine did not think that there was anything dead about cellular pathology when Rudolf Virchow poured the new wine of his vital spirit into the old bottles of tradition. And today the bottles are not yet full. After all, what is electron microscopy of diseased tissue but morbid anatomy of the minute?

Pathology had its beginnings on the autopsy table in the place unpleasantly named the dead house. Wilens opens his delightful *My Friends the Doctors* as follows: "The old adage that dead men tell no tales does not hold true as far as the medical profession is concerned. Dead men have for centuries been telling doctors the story of *how* they got sick and *why* they died, and doctors have made use of this information very effectively in the treatment of other sick people . . . The public owes to the dissectors of the dead a debt that it has seldom recognized or acknowledged."

Virchow was naturally handicapped by his ignorance of the intimate structure of cells, for he could not even guess at the existence of mitochondria, or ribosomes, or lysosomes, or genes, or DNA and RNA, which every student knows all about. And yet in 1898, four years before he died, he could write these

words: "We must strive to understand what is *happening* during a morbid process, and not be content merely with the existent condition. We must endeavour to dissect the cell, to take it apart and find out what each portion contributes to cellular function and how these parts go wrong in disease." That was seventy years ago!

The reason for the structure of an organ is the function it has to perform, so we must first correlate normal structure and function, and then try to do the same for structure and function in disease. When we succeed, we have united pathology and clinical medicine. The question the student should ask most frequently is Why? Nor should he necessarily always accept the answer of his teacher. Take for instance the question so vital in heart transplantation — what is death, and when is a person dead? To that question, the enquiring student will get different answers, depending on the teacher.

A new order of pathologist has now arisen whose duties are largely concerned with laboratory tests on living patients, so that he is known as a clinical pathologist. Of recent years, the scope of clinical pathology has increased to such an extent as to be almost unrecognizable. But the autopsy room still remains a great storehouse of new knowledge waiting to be uncovered. For centuries the thymus gland has been looked down on as largely vestigial; now it has become the most exciting organ in the body, possibly the key to cellular immune function. The object of the autopsy is not merely to determine the cause of death, but to throw light on the disease process and to explain, if possible, how the symptoms of the patient were produced.

The practice of medicine is a search for answers to three questions: What is wrong, what is going to happen, and what can be done about it? To these the pathologist adds a fourth and even more penetrating question: Why did it happen? The pathologist has to try to explain not only why the patient died, but how he was able to live with a body so maimed, disordered, and worn out. It is the high function of the pathologist not only to attach correct labels to the lesions when he sees them, but to reconstruct the course of events from the earliest inception of the disease to the final moment when we have to fall out of "the splendid procession of life", for disease may be defined as merely a summation of chemical reactions that have gone wrong.

But we must not forget that it is the whole patient who comes to consult the doctor, not just a disordered liver, a cardiac lesion, a lump in the breast, or an electrolyte disturbance. Man is more than a sum of his parts, and the student when he becomes a doctor (and not a pathologist) must remember that his vocation is to consider the patient as well as the disease. In the memorable words of Francis Peabody: the care of the patient is caring for the patient.

William Boyd

Editorial *Quantity And Quality*

As medical knowledge expands in all directions, the number of facts to be digested spirals. The point has already been reached where no one physician can possibly have anything approaching a complete knowledge of all the developments in all the branches of medicine. This state of affairs carries with it a danger and a temptation: the danger of seeing this as a conquerable challenge, and the temptation of being sucked into the impossible attempt to master all these facts. Since this has become more than a full-time occupation, the possibility presents itself for members of our profession to obsessively pursue the acquisition of medical facts to the exclusion of knowing the implications of these facts. They may even seek the route of searching for details as a means of avoiding coming face to face with the fact that the *goals* of medicine have eluded them.

We may ask, then, what *are* the goals of medicine? What do physicians actually seek to accomplish in working with their patients?

To answer this we must look at the results of our efforts, in the broadest sense. We see that physicians act to reverse, or at least to halt, the inevitable downhill process occurring in all biological organisms, which, in heightened form in specific organs or systems, earns the title "disease". It is a well-known fact that in many areas deterioration begins almost at birth; an example is the atheromatous changes in the aorta.

The objective deterioration in the patient's anatomy and/or physiology has its subjective counterpart in the suffering it causes the patient. This is hopefully relieved by the physician's intervention.

In sum, physicians can play a significant role in overcoming the disturbances which interfere with the patient's ability to achieve satisfaction in life. It is to this end that all their efforts are directed.

This basic goal of the "art and science of medicine" is all too often in danger of being lost to the younger generations of physicians. Nobody talks about it in medical school, presumably because it is too obvious. But the obvious is not always recognized. We need only remember our first clinical exposure to patients: the patient may have been cyanosed, breathing at a rate of thirty times per minute, with an immobile left chest and engorged jugular veins, yet our untrained eyes searched him carefully and found "nothing wrong". On the eve of graduation we can laugh at the thought of missing such findings. It appears, though, that nothing is so obvious that a novice will of necessity notice it. Some people are by nature shrewd observers, and able to abstract the underlying pattern from what they see; most of us unfortunately have to be guided.

Pursuing further the problem of the physician's aim — to increase maximally his patients' well-being — we may now ask how this is to be ahieved. Clearly this can be done only through an understanding of all the forces governing "dis-integrative" reactions in the human being.

The history of science in civilization has demonstrated the truth of the saying: "Knowledge is power." The power comes from the application of the knowledge to *control* natural processes, or to *alter* them, in the interest of a better life for humanity.

In medicine great advances have been made: the natural life span has increased, and morbidity from physical illness during the augmented life span has decreased. The actual quantity of life has increased, and the quantity of time during which individual people are free from organic disease has increased as well. This represents a great step forward.

But the quality of life is more difficult to improve. It involves the subjective "happiness" of people: comfort, contentment, the ability to enjoy the technological improvements in our surroundings. Telling the patient to "relax and enjoy life" is not the answer; if he knew *how* to do this he would — without us.

Physicians are constantly being admonished for not treating "the whole patient"; the reference is to their neglect of sociological and psychological factors. No doubt this is the area where greater knowledge will make possible significant improvements in the health of humanity — improvements which are subjectively felt, so that life is not only prolonged, but also, with the elimination of impediments, enriched.

M. L. Iscove

Thank You

The editors of Volume XLVI wish to extend sincere thanks to all of the individuals and organizations who have contributed their time, their energy and their financial assistance.

The Medical Society and the Medical Alumni Association deserve particular recognition for their generous support. Konrad of The Maple Leaf Press was instrumental in the production of this volume; his technical assistance was invaluable. Special thanks and congratulations are extended to Heinz Loth and his staff of artists and draftsmen without whom there would have been no pictorial aids. Bob Walker, Mike Rosenbluth, Sherryn Levinoff and Barbara Kee have kept the Journal afloat in a sea of bills through their able management of Business, Advertising, and Circulation.

The editorship of the Journal is an arduous yet highly rewarding task; we wish the newly appointed editors-in-chief, Gord Hardacre and Titus Owolabi, all possible success in the adventure which is to befall them.

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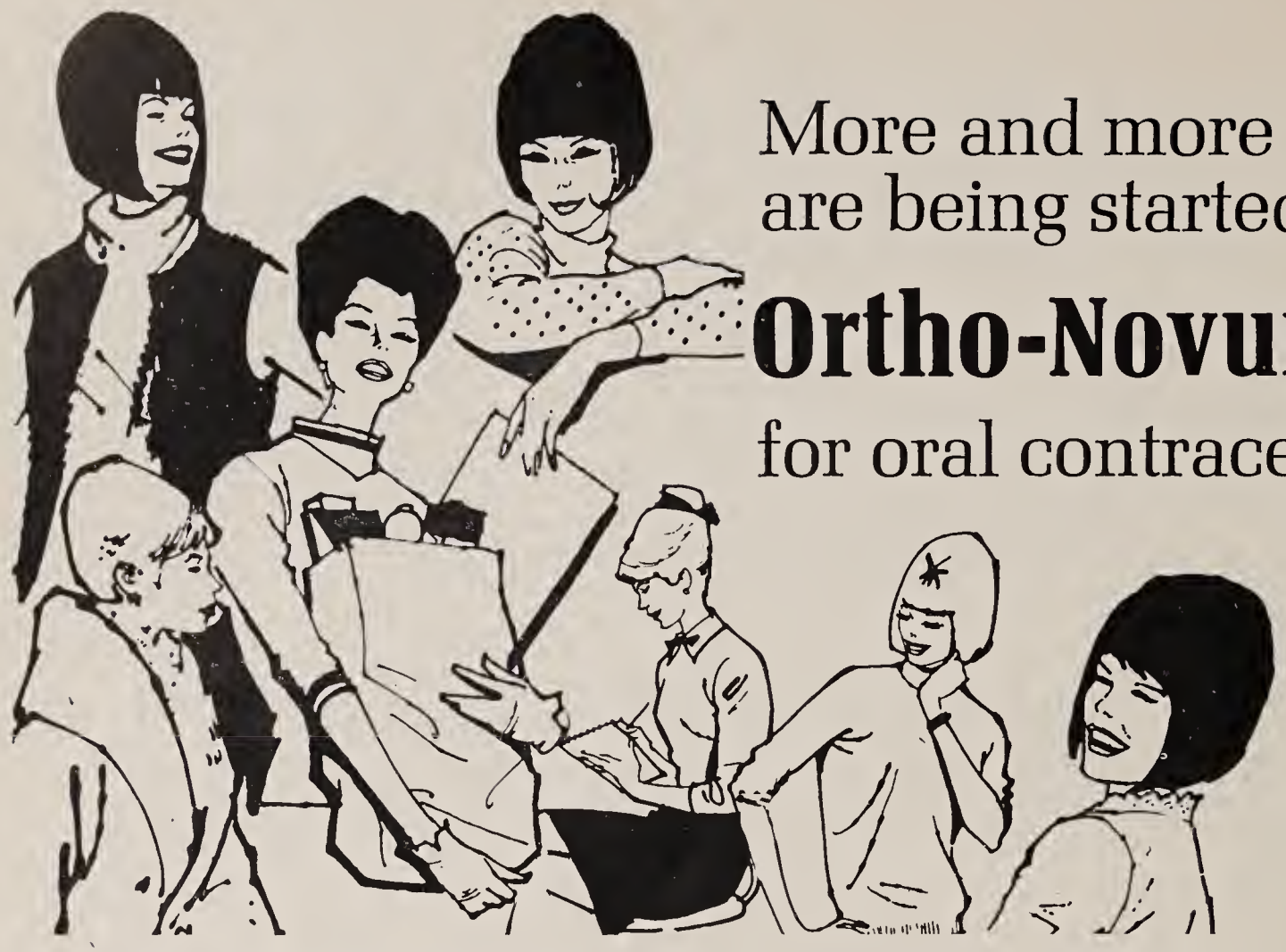

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Student Research

Spleen Colony Techniques In Hematology

Over the past 9 years at the Ontario Cancer Institute, an experimental technique, the spleen colony technique, has been developed as an aid to the study of hemopoiesis. Briefly and basically, the technique involves the following: the cells of the hemopoietic system of a mouse may be destroyed by heavy whole body irradiation — the system may then be repopulated with healthy hemopoietic tissue cells (such as bone marrow) from isologous mice, by injecting these cells intravenously into the irradiated mice. One manifestation of this repopulation is the formation of visible lumps, or colonies, of new hemopoietic tissue in the spleen. These colonies of cells of the non-irradiated donor mice are quite discrete from surrounding splenic tissue and examination of them has shown several features: they are derived from a single cell which can be assumed to be a hemopoietic stem cell, or the original precursor of all the blood cells; and after only 10 days of growth, they may contain up to one million cells of the various blood cell types (erythrocytic, granulocytic, megakaryocytic or mixtures of these).

Thus each colony has the properties of a small but actively functioning hemopoietic system, located in an environment which may be manipulated fairly readily in order to study the system. In this manner, many interesting phenomena concerning hemopoiesis have been discovered.

There must be some control mechanisms determining the relative production rates of erythrocytes and of granulocytes by the system. If a group of mice is rendered plethoric by repeated whole blood transfusions, then blood levels of erythropoietin drop to become negligible. If these mice are irradiated, then given isologous bone marrow by the normal technique, spleen colonies form in them with normal frequency. Microscopic examination shows the colonies to be deficient in erythrocytic elements and consisting mainly of granulocytic cell types. It is thought that there exists an early differentiated cell, the erythropoietin sensitive cell, which proliferates and differentiates to erythrocytes only in the presence of suitable blood levels of erythropoietin. Thus erythropoietin would control erythropoiesis, as is demonstrated using the spleen colony technique.

One strain of mice with an identifiable genetic change, is always anemic — its hemopoietic cells will not form colonies in other mice, implying a genetically determined loss in proliferative capacity of their stem cells. Other genetic and humoral factors affecting rate and form of hemopoiesis are being studied and hopefully, research will progress either with modifications of the original technique or with new techniques until all stages of hemopoiesis and the factors controlling them are understood.

T. V. Allen, B.Sc. 7T0

Atopic Respiratory Diseases

E. Keystone 6T9

A. GENERAL

1. Definition

Atopy, derived from the Greek δΠσΠσς means out of place, strange or odd (1). The term is generally applied to a condition of rhinitis, asthma or infantile eczema seen in individuals who are allergic to pollens and other airborne allergens. These atopic conditions may occur singly or in combination in a given individual. Almost invariably it is found that the same conditions also affect other members of the same family.

2. Incidence

It is estimated that 10% of the population in the parts of the U.S.A. where ragweed is common is affected at some period of life by definite atopic diseases[2]. The incidence of asthma and hayfever is approximately the same, and each disease occurs with equal frequency in males and females. Clinical experience has shown that asthma and hayfever frequently occur in the same person. Most authors estimate that asthma occurs in approximately 40% of persons having hayfever. Contrary to what has generally been accepted, hayfever does not commonly lead to asthma. In one study, 75% of persons having both diseases had asthma alone initially or the two appeared within the same year of onset[3]. Moreover, only 5 - 10% of persons with hayfever subsequently developed asthma.

3. Heredity

Weiner, Zieve and Fries suggest that the predisposition to atopic allergic disease may be transmitted by means of a single pair of allelomorphic genes, H and h in which H determines non allergy and h determines allergy[2]. Three different genotypes are possible: HH non-allergic individuals, hh allergic individuals whose symptoms are prone to begin prior to puberty, and Hh individuals who may be normal transmitters or develop allergic disease after puberty. This theory agrees well with such family data as are available.

It should be emphasized here that hereditary predisposition alone is not a sufficient cause of sensitivity since contact with the allergen is necessary for expression. Also, contact in the absence of a hereditary predisposition is not sufficient, for it has been found that contact with the allergen in general will not render a normal person atopic[1].

B. PATHOLOGY

1. Allergic Rhinitis

In allergic rhinitis the subepithelial connective tissue is the site most effected. Edema due to an increased vascular permeability leads to the occlusion of nasal passages and to the characteristic pale boggy nasal mucosa. There is also hypersecretion of mucous which is reflected in epithelial hyperplasia, particularly of goblet cells. Massive numbers of eosinophils accumulate in the connective tissue and migrate through the epithelium. It is the presence of these cells in nasal secretions which is suggestive of allergic rhinitis. However, eosinophilia may be seen in other conditions and hence is not diagnostic of atopic allergy. Excessive edema beneath the thin and poorly supported nasal epithelium occasionally produces areas of mucosal prolapse which are recognized as nasal polyps.

2. Atopic Asthma

The pathology of atopic asthma is essentially the same as that of allergic rhinitis. However, the consequences are strikingly different since the changes occur in the small bronchi and include bronchial smooth muscle contraction. Lung specimens of patients who die during an asthmatic attack reveal hyperinflated lungs and widespread bronchial obstruction by mucous plugs. These plugs are composed of viscous mucous containing eosinophils and shreds of epithelium.

The bronchial wall mucosa may be thrown into folds during an attack, in part due to subepithelial edema and in part to bronchial muscle spasm. As in rhinitis, the presence of an abnormally large proportion of goblet cells reflects the mucous hypersecretion. Houston et al[4] noted the detachment of large sheets of surface epithelium leaving only the basal cell layers. This desquamation results in the loss of many ciliated epithelial cells which function normally in propelling the mucous upward. The loss of cells leads to pooling of secretions and more severe ventilatory impairment. As in rhinitis the subepithelial connective tisσue iσ edematous and infiltrated heavily with eosinophils. Finally, there is an increase in smooth muscle bulk around asthmatic bronchi due to hypertrophy and/or spasm.

C. IMMUNE MECHANISM

1. General

Like all allergic phenomena, atopic respiratory allergy results from an antigen-antibody interaction. The sequence of events giving rise to changes in atopic respiratory allergy resulting in the symptoms are: a) initial exposure of the individual to the specific antigen, b) formation of antibodies as a result of this exposure (immunization), c) fixation of the specific antibodies to the tissue (sensitization), d) re-exposure to the specific antigen, e) antigen-antibody union in the tissue, f) release of pharmacologically active mediator materials, among which are histamine, serotonin and SRS-A and g) action of these materials on the various end organs such as smooth muscle of vessel walls.

TABLE I. IMMUNOGLOBULINS

Immunoglobulin (Ig)	IgA	IgD	IgE	IgG	IgM
Molecular weight (approx.)	$16x10^4$	$16x10^4$	$16x10^4$	$16x10^4$	$1x10^6$
Concentration is serum (gms %)	0.05-0.2	20.04	?	0.8-1.5	0.04-0.12
Electrophoretic mobility	slow β	fast δ	slow β	mid δ	fast δ
Carbohydrate content (mgms %)	10-12	?	?	2.5-3.5	10-15
Capacity to cross placenta	0	?	0	+	0
Capacity to activate anaphylaxis	0	?	+	0	0
Capacity to fix complement	0	?	0	+	+
Heavy chains	δ	δ	ϵ	δ	μ
Light chains	K&λ	K&λ	K&λ	K&λ	K&λ

If the allergen is injected intravenously, an atopic individual reacts with a typical anaphylactic shock. There is no reason then to regard atopy as different from anaphylaxis. Atopic respiratory disease has the same pathophysiology as anaphylaxis except that the changes are localized to the respiratory tract, either in the nasal mucosa, or bronchus or both.

2. Antibodies

The basic element in atopy is the reaginic antibody. Reaginic (skin-sensitizing) activity has recently been characterized by K. Ishizaka and found to be associated with a new class of immunoglobulins, named IgE[6]. Immunoglobulins are a system of related proteins which encompass all known types of antibodies. They are a heterogenous group, both physically and chemically. To date five major classes of immunoglobulins have been characterized (TABLE I). Each protein consists of high and low molecular weight chains of amino acids. The chains are designated respectively as heavy and light. Since the light chains in each of the classes are essentially the same, the heavy chains determine the differences in immunological and physiochemical properties.

Ishizaka based his conclusion concerning the association of reagin and (immunoglobulin) E on the following facts: 1) reaginic activity was precipitated by antibodies directed against IgE globulin, but not by antibodies specific for the other 4 immunoglobulin classes, 2) distributions of reaginic activity and of IgE parallel on fractionation of patients' sera by anion exchange column chromatography, gel filtration, ultracentrifugation and zone electrophoresis, 3) IgE fraction of sera possessed high reaginic activity which was removed subsequently by anti-IgE[6].

A second type of antibody of the IgG class, often coexists with reagin and is specific for the same antigen. To date only the IgE, but not the IgG antibody of the same specificity has been shown to mediate the anaphylactic atopic reaction in humans. On the other hand, the IgG antibody combines more strongly with the antigen than does the IgE antibody. Under limiting conditions of antigen this preferential binding to IgG can block the interaction of the antigen and IgE antibody. Since this could result in inhibition of the anaphylactic reaction, the IgG antibody is sometimes referred to as the blocking antibody.

One concept of the basis of atopic respiratory disease relates to a balance between IgE and IgG antibodies of the same specificity. When IgE dominates the individual is likely to have symptoms on exposure to antigen while the tendency is diminished when there is a dominance of IgG antibody. Most studies carried out to examine this concept have failed to support it, suggesting that additional factors must also be involved. There is not yet a complete understanding of the mechanism involved in atopic respiratory disease.

3. Allergens

The term allergen is applied specifically to those antigens which cause allergic symptoms. The allergens in atopy are contacted predominantly by inhalation and ingestion.

a) *Inhalant Allergens*

Certain wind-borne plant pollens, mold spores and insect parts are spread in sufficient quantities over large areas to cause predisposed individuals to develop atopic rhinitis or asthma. In addition, animal danders, house dust or other inhalants provide local contamination at home or work. Of these, plant pollens are the principal offenders, ragweed being the commonest in this area.

b) *Ingested Allergens*

Food allergy appears to be encountered more commonly in children than in adults. Cow's milk is the most frequently suspected food allergen. Other relatively common food allergens include fish, nuts, fruits, egg and wheat products.

4. Cell Released Mediators

In recent years, several chemical mediators of allergic reactions have been identified, including histamine, slow-reacting substance of anaphylaxis (SRS-A), and serotonin.

a) *Histamine*

Histamine is considered to be important because its pharmacological effects include increased vascular per-

meability and contraction of bronchiolar and other smooth muscle. These properties could account for the changes seen in atopic rhinitis and atopic asthma. Also, histamine is stored in mast cells and has been released in vitro from sensitized human lung and leukocytes on exposure to antigen [Schild et al, 1951[7]; Lichtenstein & Osler, 1964[8]; Parish 1967[9]]. However, since asthma on the whole does not respond well to antihistamines and rhinitis responds variably it is generally believed that there are other important mediators operating.

b) *SRS-A*

SRS-A is capable of contracting smooth muscle and hence may be partly responsible for bronchospasm in asthma. Unlike histamine, SRS-A does not appear to be stored in tissue, but forms more slowly during an antigen-antibody interaction. It is worthy of note that antihistamine drugs do not antagonize the effects of SRS-A. SRS-A may account then for certain of the antihistamine resistant features of atopic respiratory allergy.

c) *Serotonin*

Serotonin has been demonstrated in the gastrointestinal tract and brain of most mammals and occurs variably in the lung, skin, leukocytes, mast cells and platelets. In humans serotonin was shown to be released from actively sensitized platelets but not from lung and leukocytes following antigen exposure. Also, this substance is relatively inactive in man in increasing vascular permeability and stimulating smooth muscle contraction. It appears unlikely then that serotonin is important in atopic respiratory disease.

D. CLINICAL PRESENTATION

1. History & Physical Examination

a) *Atopic Rhinitis*

Atopic rhinitis is a syndrome of sneezing, watery discharge and nasal obstruction[5]. The term hayfever has been generally applied to seasonal paroxysmal attacks caused by ragweed pollen, but it may also be applied to nasal symptoms produced by other pollens, molds, house dust and animal dander. Depending on the inciting agents, symptoms may be seasonal or perennial.

On physical examination, the nasal mucosa usually appears to be swollen, light blue or pearly gray in colour and covered by a mucoid discharge. Polyps may be seen on nasal examination. If the sinuses are affected, there will be clouding or opacification on transillumination.

b) *Atopic Asthma*

Atopic asthma is characterized by paroxysms of dyspnea, wheezing and coughing[5]. The symptoms are made worse by anxiety, and are aggravated by respiratory irritants such as cigarette smoke and other fumes. During recovery the cough is more productive, yielding a sputum which is frothy, white and mucoid. There are usually no systemic manifestations of this disease.

Periodicity of the manifestations is the rule. Affected individuals tend to be worse on awakening and gradually improve during the morning. Also, most feel worse when recumbent. Superimposed infection may result in the production of a purulent sputum.

On inspection, the patient is seen to be wheezing and struggling for breath. Auscultation yields whistling and wheezing sounds which are more pronounced on expiration; also the expiratory phase is prolonged. Scattered rales are occasionally heard. In long standing asthma, chronic obstruction of air passages may lead to emphysema.

2. Skin Testing

Skin tests detect the presence of atopic reagin in skin. The appropriate allergenic material is introduced into the patient's skin and a wheal and flare response develops rapidly in the presence of the specific skin-bound reaginic antibody. Skin testing may be performed by scratching or pricking the skin or by injecting the antigen intradermally. The intracutaneous test is more sensitive than the scratch test.

The problem faced by the physician in interpreting the skin test can be summed up as follows: a positive skin test provides diagnostic support in the presence of a history consistent with allergy to the test material. However, a positive test alone does not indicate clinical sensitivity in the absence of a history consistent with this. Skin tests are also useful in a negative sense, in excluding allergy as a cause of symptoms when the appropriate skin tests are negative.

Skin tests are not diagnostic but confirmatory. It is the clinical assessment which remains the prime tool in ascertaining the effect of a particular allergen.

A part of the skepticism concerning skin testing has come from the injudicious use of a multitude of allergens most of which could be eliminated on the basis of a clinical appraisal. This practice has led to unnecessary discomfort and expense for some patients. In the majority of allergic individuals satisfactory information can be obtained by doing selective testing with a small number of antigens relevant to the requirements of the case in question.

E. TREATMENT

1. Avoidance of Allergens

a) *Ingestants*

Avoidance of ingested allergens is self-explanatory.

b) *Inhalants*

Certain allergens such as animal danders and feathers can be readily avoided. The pollens are more difficult to avoid, but this may be possible in the case of some, such as ragweed, which do not exist in Northern Ontario. Molds and house dust are the most difficult to avoid and the only feasible approach to these is to avoid situations in which either is likely to be highly prevalent.

2. Injection Therapy

Injection therapy consists of administering increasing amounts of a specific allergen at intervals until a maintenance dose is reached. The maintenance dose is continued for a variable interval ranging from 2 years and on. Injection therapy is used almost exclusively with inhalant allergens.

Studies by Lowell and Franklin[11 12] and Norman et al[13] demonstrated that those individuals receiving injection therapy with ragweed pollen in the treatment of atopic rhinitis reported fewer symptoms during the pollen seasons than those receiving a placebo. Proof of efficacy is less well substantiated in the case of other allergens used for injection therapy such as house dusts and molds. One recent study showed that treatment with house dust extract was totally ineffective in ameliorating asthma symptomatology[14].

The level of blocking antibody increases with injection therapy, but this does not relate directly to the results of treatment. The mechanism then, by which relief of symptoms is achieved is still obscure. The data also demonstrate that desensitization per se is not involved. Hence the term injection therapy is preferred to that of desensitization.

3. Symptomatic Relief

a) *Atopic Rhinitis*

(i) Antihistamines

Antihistamines antagonize histamine by competing for the same site of action. The relief of itching, sneezing and running of the eyes obtained with an antihistamine is not lasting and hence the drug must be taken over the entire course of the illness.

(ii) Vasoconstrictors

Vasoconstrictors reduce the edema of the nasal mucosa, thereby shrinking the membrane and providing a clear nasal passage. Physicians have noted a secondary rebound effect following the use of these drugs which leads to an increase in edema within an hour or two. Moreover, vasoconstrictors exhibit tachyphylaxis, that is, a reduced effect with each successive dose.

Topical

The most rapid effect is produced by epinephrine hydrochloride in a 1:1000 solution[15], but its action is brief and its secondary effect is marked. More frequently used is a 1% solution of ephedrine sulphate. If one has to use a vasoconstrictor, and most allergists are opposed to their use, phenylephrine hydrochloride in 0.25 or 0.5% strength is the safest. It is the most common ingredient of commercial drops and sprays.

Oral Decongestants

The most widely used oral decongestant is ephedrine sulphate in 15 to 50 mgm dosage. Another favourite oral vasoconstrictor is known as pseudoephedrine. It must be noted that oral decongestants exhibit the same amount of rebound vasodilating action as topical constrictors.

(iii) Corticosteroids

Oral corticosteroids provide effective relief of nasal symptoms. Since hayfever is of limited duration there may be justification for using this type of agent at the height of the pollinating season, if the symptoms are severe and cannot be relieved by any other means. However, corticosteroids should be used with extreme caution in this condition because of the potential serious side effects.

b) *Atopic Asthma*

(i) Bronchodilators

Subcutaneous & Intravenous

Acute attacks may be promptly relieved by a 0.3 to 0.5 ml subcutaneous injection of epinephrine HC1 diluted 1:1000[15]. This dose may be repeated at 20 minute intervals for several doses. If epinephrine is not effective, aminophylline in a 250-500 mgm dose may be given by slow intravenous infusion or by suppositories. Parenteral therapy of this kind is reserved for rapid relief of acute distress.

Oral Agents

Ephedrine in doses of 25 mgm 3 times per day is the most common oral agent used. Aminophylline is much less effective orally and must be given in comparatively large doses of 500 mgm every 6 hours. Isoproterenol is reported to be effective sublingually in 10 - 15 mgm doses and has been compounded in cough syrup for bronchospastic conditions.

Aerosol

Inhalation of epinephrine diluted 1:100 and isoproterenol in a dilution of 1:100 are known to provide effective bronchodilation. There have been cases reported however, in which these nebulized medications perpetuated bronchospasm owing to an irritative effect.

(ii) Expectorants

Expectorants are useful in thinning the viscous mucoid secretions coating the bronchial walls. The simplest and most effective method for loosening mucous is adequate hydration. Asthmatics should consume one glass of liquid during each waking hour. Steam inhalation, a simple home procedure, often acts as an excellent liquefier and expectorant.

Iodides are the most important drugs to facilitate expectoration. They are usually prescribed as the saturated solution or the enteric coated tablets. Glyceryl guaiacolate is another expectorant often compounded in a mixture.

(iii) sedation

The asthmatic requires sedation for several reasons: 1) he has taken repeated doses of sympathomimetics

which make him jittery and shaky; 2) he is usually apprehensive because of gasping for air. The safest sedative is a small dose of barbiturate or chloralhydrate. Morphine is contraindicated because of its depressant effects on the respiratory centre. Moreover all sedatives must be used with extreme caution because of their potential for respiratory depression.

(iv) ADRENOCORTICOSTEROIDS

The mode of action of corticosteroids is not well understood but it is generally agreed that their immediate effect is due to a suppression of the allergic inflammatory response in susceptible tissues[5]. These drugs frequently produce dramatic relief of otherwise uncontrollable and incapacitating symptoms. If oral steroids are given, a lag of 24 to 36 hours occurs before there is a sufficient level in the body to affect relief of symptoms. A large dose of 40 mgm prednisone per day is given initially and gradually withdrawn over 1 to 2 weeks or reduced to a maintenance level of 10 mgm or less. Parenteral steroids may be used to provide a more rapid response.

(v) ANTIBIOTICS

In acute asthmatic attacks which persist for several days, the sputum should be cultured and antibiotics administered as a rule, particularly if the sputum is mucopurulent. Successful management of the chronic asthmatic patient also requires the use of broad-spectrum antibiotics promptly for each upper respiratory infection. Antibiotics such as tetracycline or ampicillin in 250 mgm doses every 6 hours are generally effective in controlling infection.

(vi) MISCELLANEOUS DRUGS

In the past year several favourable reports on the treatment of asthma with a new compound, disodium chromoglycate have appeared. This substance has no intrinsic bronchodilator activity, but appears to be a specific inhibitor of reaginic antigen-antibody mechanisms[16]. In atopic volunteers there was a reduction of the bronchospasm induced by aerosol of the appropriate antigen when disodium chromoglycate was administered by inhalation previous to challenge. Recent studies demonstrated an improvement in a moderately large percentage of asthmatic patients.[17]

4. PSYCHOTHERAPY

There is no question that emotional problems have a profound effect on the symptoms of asthma. Psychiatric texts admit that the hypersensitivity mechanism must be present before emotional difficulties will cause asthmatic attacks. Psychiatrists have even gone so far as to interpret the wheezing as a suppressed cry for the mother figure, an unverbalized expression of so-called separation anxiety[10]. In a recent study of interpersonal relations between asthmatic children and their families, no correlation was found between emotional disturbances in the family and the development or severity of asthma in children[19]. However, this does not deny the importance of psychiatric therapy, both formal and superficial.

F. SUMMARY

Atopic rhinitis and atopic asthma occur on the basis of hereditary predisposition. The basic element in atopy, the reaginic antibody, interacts with its corresponding antigen to release pharmacological substanees which include histamine, serotonin and SRS-A.

Clinical assessment, skin testing, and sputum and nasal smear examination are the prime tools of diagnosis. Skin testing, despite certain weaknesses is considered a valuable confirmatory test.

Treatment consists of avoidance of allergens, injection therapy, symptomatic measures and psychotherapy.

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Sarcoidosis

S. Parker 6T9

DEFINITION

J. G. Scadding defines sarcoidosis in terms of its histological appearance and distribution avoiding any implications as to its etiology. He defines sarcoidosis as a disease characterized by the presence in all of several affected organs or tissues of epithelioid cell tubercles without caseation, though some fibrinoid necrosis may be present at the centres of a few tubercles, proceeding either to resolution or to conversion of the epithelioid cell tubercles into avascular, acellular hyaline fibrous tissue. The central feature of this definition is not the non-caseating tubercle, for this in itself is not diagnostic: tuberculosis, fungal infections, beryllium disease and local 'sarcoid' reactions (eg. to foreign bodies such as silica and to such infiltrating processes as malignancy and Hodgkin's disease) must be excluded. What is diagnostic of sarcoid is the monotonous recurrence of these non-caseating tubercles throughout all the affected organs or tissues. In addition, organs most frequently involved are the lymph-nodes, lungs, liver, spleen, skin, eyes, small bones of the hands and feet and the salivary glands, although nearly every organ or tissue has been reported to have been involved.

INCIDENCE AND EPIDEMIOLOGY

Information regarding the incidence of sarcoidosis is incomplete even for the most intensively studied communities. There are several reasons for this. One is that since many cases are so benign in their course, many individuals must pass through the whole course of the disease without consulting a doctor. Another is the use of a variety of techniques (Kveim test, x-ray, biopsy) and the lack of uniform standards employed in arriving at a diagnosis. A third reason is that the clinical manifestations of sarcoidosis are so varied that a patient may first come to the attention of any one of a number of specialists, in which case the incidence might vary with the frequency of the presenting symptoms. However, sufficient information is available to indicate some important differences in the incidence of the disease.

Data derived from mass radiography in Britain gives incidences varying from 5 to 19.8 per 100,000 population. The rate appears to be higher in females than males (eg. British Ministry of Health Report 1960 gives rates of 19.8 per 100,000 in females and 14.4 per 100,000 in men). Higher rates in Sweden have been reported. (Lofgren (1957) reported cases of 30 per 100,000 in men and 50 per 100,000 in women.)

The peak incidence in both sexes appears to be around the age of 25 - 30 and most patients are between 20 and 40 years of age. However, patients with symptoms beginning as early as age 7 and as late as age 74 have been reported.

The incidence in American negroes has been reported as high as 17 times that in whites. The disease has been described in family groups but there is no evidence for communicability.

Distribution of the disease is world-wide, with the highest incidence in the temperate zone, especially in the Southeastern United States. Epidemiologic studies suggest a possible relationship between exposure to pine pollen and clinical sarcoidosis.

ETIOLOGY

The hypotheses that have been advanced about the etiology and pathogenesis of sarcoidosis are listed below:

1. That sarcoidosis is an unusual reaction to a mycobacterial infection, ie. a form of tuberculosis. There is a similarity between the histological and clinical changes of sarcoidosis and tuberculosis. Arguments in favour of regarding sarcoidosis as a non-caseating variant of tuberculosis are as follows:

a. Sarcoidosis and bacteriologically proved infection with M. tuberculosis are frequently associated.

b. Non-caseating tubercles indistinguishable from those associated with sarcoidosis have been found in undoubted cases of mycobacterial tuberculosis.

c. No clear line of demarcation can be drawn between sarcoidosis and certain cases in which a diagnosis of tuberculosis with low tuberculin sensitivity is appropriate.

d. Substances not normally present in mammalian tissue but present in certain bacteria, including mycobacteria, have been identified in extracts of sarcoid tissue.

e. Some workers have found that a high proportion of patients with sarcoidosis have a history of contact with tuberculosis.

Arguments against the role of M. tuberculosis infection as a factor in causation of sarcoidosis include:

a. The proportion of cases of sarcoidosis from which tubercle bacilli are isolated is very small.

b. The association of mycobacterial infection with sarcoidosis may be due to predisposition to such infection.

c. Tuberculin sensitivity is lower in groups of patients with sarcoidosis than in unselected members of the population from which they are drawn.

d. The common patterns of organ involvement in sarcoidosis differ from those in tuberculosis.

e. Detailed epidemiologic studies have shown discrepancies between the geographic distribution of sarcoidosis and tuberculosis.

f. Antituberculous chemotherapy does not influence the course of sarcoidosis.

2. That it is due to a specific but at present undetected infective agent. However, attempts to isolate an agent specific for sarcoidosis have been unsuccessful.

3. That it is due to exposure to some specific but not infective factor. Pine pollen has been suggested as a possible agent, but no definite relationship has been established.

4. That it should be classified with the collagen diseases. The suggestion that sarcoidosis should be regarded as a hypersensitivity granuloma analogous with polyarteritis nodosa does little more than indicate a general line of thought.

5. That it is dependent upon an immunologically determined alteration of reactivity of a peculiar sort, to which certain individuals may be especially prone; and that in individuals liable to this type of altered reactivity, sarcoidosis occurs in response to certain specific agents. This host state could be a result of genetic susceptibility or unidentified factors of hypersensitivity.

PATHOLOGY

There are great variations in the extent of dissemination and in the degree of involvement of any organ. In some instances the disease is limited to scattered lesions occuring in perhaps a few lymph nodes. In others it may be widely distributed throughout the body, producing miliary nodules in many organs or tissues. Occasionally large tumour-like masses, limited to one or several organs are seen. Most commonly, the disease is first localized in the tracheobronchial lymph nodes. From this site, lesions develop in the lungs possibly by retrograde dissemination from hilar lymph nodes or by hematogenous spread to other areas of the body.

Earliest gross changes are tiny gray or yellow granules which simulate the lesions of miliary T.B. These may be clustered together as large isolated pale patches which on close inspection are made up of many closely packed minute granules. Lesions of this type are frequently seen on cut surfaces of lymph nodes, spleen or liver.

Histologically the disease is characterized by the formation of epithelioid cell tubercles, well circumscribed within the surrounding tissue in the early stage, with a few lymphocytes situated peripherally. The tubercle of sarcoid differs from that of T.B. in so far as it does not caseate centrally. Sarcoid tubercles heal by scarring, becoming converted into avascular, acellular hyaline fibrous tissue.

Giant cells are frequently associated with the sarcoid tubercle and often contain concentrically layered masses containing calcium and iron (Schaumann bodies) and crystal shaped protein rosettes (asteroid bodies). The composition and properties of Schaumann bodies are identical in sarcoidosis, beryllium disease and tuberculosis.

Sarcoid granulomata have been observed in certain forms of Hodgkin's disease, in ovarian tumours and in regional nodes draining various forms of carcinoma. Autopsy studies have revealed that involvement of lymph nodes thought at biopsy to have been caused by sarcoidosis could not be differentiated from Hodgkin's disease, lymphosarcoma, histoplasmosis or non-caseating tuberculosis. Thus, the histology of sarcoidosis while helpful clinically cannot be considered as unequivocal proof of the diagnosis.

CLINICAL MANIFESTATIONS

First sign or symptom in 275 cases of sarcoidosis (from Scadding 1967):

Lung changes:	
abnormal radiograph	94
respiratory symptoms	76
Erythema nodosum	31
Febrile arthralgia	8
Constitutional symptoms:	
lassitude, malaise	9
fever	3
Ocular symptoms	27
Skin lesions:	
sarcoids or lupus pernio	11
subcutaneous nodules	1
infiltration of vestibule of nose	1
infiltration of scars	2
Superficial lymphadenopathy	10
Grossly enlarged spleen	1
Heart block	1
	275

CHANGES IN THE RESPIRATORY SYSTEM

The most frequent early sign of sarcoidosis is an abnormal chest radiograph. There is evidence that sarcoid tubercles may involve the lungs and even be widely scattered in the lungs without causing either clinical or radiographic evidence of their presence during the whole of their course to resolution.

Scadding has divided the pulmonary history of the disease into three phases on the basis of radiographic appearance (a) Bilateral Hilar Lymphadenopathy (BHL); (b) Pre-fibrotic; and (c) Fibrotic Stages.

BILATERAL HILAR LYMPHADENOPATHY (BHL)

BHL is a frequent initial sign of sarcoidosis and may be accompanied by no symptoms, vague disturbances of health, non-specific respiratory symptoms, low grade fever, febrile arthralgia or erythema nodosum. BHL nearly always precedes other manifestations that may develop. Changes in the lungs and eyes tend to follow

closely on BHL whereas sarcoid of the skin tends to appear later.

Within 2 years, and usually within one year, enlarged hilar nodes return to normal size. When BHL subsides spontaneously and completely, it is extremely rare for further manifestations of sarcoidosis to appear, although previous radiographic lung changes may persist.

On X-ray the lymph node enlargement usually appears symmetrical. The right side may appear slightly larger due to the left hilar shadow being obscured by the left border of the heart shadow. The outer border is clearly defined with multiple smooth contours. Tomography can be used to distinguish between shift enlargement of hilar shadows due to dilation of a main bronchus or main branches of the pulmonary vessels and enlargement of lymph nodes. Foci of calcification may be evident in the enlarged nodes, but are probably present before the sarcoid enlargement developed.

Symptoms of BHL are prolonged, vague ill health, tiredness, loss of weight, dry cough, dyspnea on exertion and chest pain which is not severe and is usually referred to the side of the chest.

Other causes of hilar node enlargement such as T.B., Hodgkin's disease, lymphosarcoma, metastatic malignancy, usually do not produce symmetrical bilateral enlargement, nor are the margins and contours of the individual nodes well defined.

Bronchoscopy in patients with BHL may show some mucosal thickening and distortion of the major bronchi if the nodes are very large, but generally there is no specific change.

PRE-FIBROTIC STAGE

In the earliest stage of lung involvement sarcoid tubercles are scattered in the lung, especially in alveolar walls, around vessels and bronchi, and in bronchial mucosa. This stage can exist up to two years without becoming fibrotic and until fibrosis starts complete resolution with disappearance of mottling from the radiograph can occur. The pre-fibrotic stage may be accompanied by enlargement of hilar nodes on both sides, but usually BHL is subsiding as sarcoid infiltration is starting.

The early radiographic appearances are many and varied, but generally consist of a widespread mottled shadow with individual rounded opacities with poorly defined margins less than 5 mm in diameter distributed more or less uniformly throughout the lungs, the middle lobe being most affected. Both lungs are usually equally involved, although the process may be confined to one lung, usually the right.

Symptoms associated with the pre-fibrotic stage are usually trivial i.e. tiredness, lack of energy, loss of weight, slight dyspnea on exertion and dry cough, with a predisposition to intercurrent acute respiratory infections.

FIBROTIC STAGE

In some patients, the pre-fibrotic stage fails to resolve and insidiously tends towards fibrosis. Dyspnea and radiographic changes develop, but are not necessarily correlated. Dyspnea may develop with advancing fibrosis before there is much change in the radiographic picture or conversely a dense and widespread infiltration may develop some local fibrosis early, while the rest resolves, causing very few symptoms. The longer infiltration persists the more likely is fibrosis and if resolution is to be complete, radiographic shadows usually start to regress in one year.

The radiographic picture of the fibrotic stage is almost pathognomonic. The middle zone mottling becomes denser while that at the apices and bases diminishes. Dense shadows appear near the hila with strand-like linear opacities spreading out from them into the upper parts of the middle zone accompanied by a distortion of vascular patterns.

Patchy fibrosis may also be widespread throughout the lungs, the x-ray showing irregular dense shadows.

The most important symptom of the fibrotic stage is dyspnea on exertion. Cough is frequent and is usually dry. A severe extensive fibrosis may lead to bronchial hypersecretions often with secondary bacterial infection. Such additional pathology may precipitate episodes of congestive heart failure. Evidence of right ventricular hypertrophy is often found in longstanding cases of extensive fibrosis in sarcoid of the lungs. Deaths may occur from respiratory insufficiency during an intercurrent infection.

CHANGES IN PULMONARY FUNCTION

Disturbances in pulmonary function are common in sarcoidosis and are related to the extent, location and duration of the disease. BHL alone leaves pulmonary function unaltered.

With sarcoid infiltration both in the fibrotic and pre-fibrotic stages, lung volume is diminished. As fibrosis develops, lung compliance and gas diffusing capacity also tend to fall, but gas diffusing capacity tends to fall earlier than compliance. There may also be an increased residual volume and spirographic evidence of airway obstruction and impaired extrapulmonary gas mixing. In some cases of infiltration diffusing capacity may not return to normal despite radiologic clearing.

DIFFERENTIAL DIAGNOSIS OF PULMONARY SARCOIDOSIS

The following conditions should be considered in the differential diagnosis of pulmonary sarcoidosis:

Infiltration with BHL:

- Hodgkin's disease
- lymphangitis carcinomatosa

Infiltration alone:
- miliary T.B.
- pneumoconiosis
- 'farmer's lung'
- histocytosis X

ERYTHEMA NODOSUM AND SKIN LESIONS

Erythema nodosum is a frequent presenting sign of sarcoidosis and is often associated with a prodromal malaise and arthralgia of several days duration. The rash consists of rounded or oval slightly raised tender nodules in shin and subcutaneous tissue occuring mostly on the shins; they are also found on the ankles, dorsal surfaces of the feet and calves and may spread over the knees to the lower thighs. The distribution tends to be symmetrical. The eruption lasts from one to six weeks while the constitutional symptoms may last for several months. Flitting arthralgia may precede erythema nodosum by several weeks and continue for several weeks after its appearance.

Erythema nodosum is not a specific manifestation of sarcoidosis and other causes must be excluded. Erythema nodosum of primary tuberculosis may be accompanied by evidence of primary tuberculous infection in the chest and fairly high skin sensitivity to tuberculin. When erythema nodosum is associated with coccidioidomycosis and histoplasmosis, skin sensitivity to the appropriate antigen will also exist. In cases due to hemolytic streptococcal infection there may be a rising ASO titre. Erythema nodosum accompanied by BHL with absent or low tuberculin sensitivity and no evidence of preceding streptococcal infection strongly suggests sarcoidosis.

Specific skin manifestations of sarcoidosis are a feature in only a minority of the cases. The lesions tend to be more common in females than males. Several types have been described. Sharply defined papules or nodules symmetrically distributed over the face, shoulder and extensor surfaces of the arms are the most common. Deeply seated subcutaneous nodules varying from 1 to 4 cm in diameter have also been described. They develop slowly on the trunk and legs and are without subjective symptoms. A third type called lupus pernio, consists of smooth 'chilblain-like' swellings of the face or digits of either the hands or feet. The affected parts are swollen, livid purple-red with a shining surface often with dilated venules, especially over the tip of the nose which often tends to be bulbous. The fingers and toes frequently have cystic bone changes when this variety of skin lesion is present.

OCULAR CHANGES

Approximately 10% of the patients in Scadding's series presented with uveitis but, while 14% developed a uveitis during the course of the disease, it is worthwhile to remember that only a small percentage of patients with uveitis of obscure cause actually have sarcoidosis. Both the anterior part of the uveal tract, giving rise to a subacute or chronic iridocyclitis and the posterior part with choroidal and retinal changes may be involved.

Symptoms of watering and redness, aching, occasionally photophobia associated with circumcorneal ciliary congestion are typical of iridocyclitis. Keratic precipitates in the anterior chamber, tending to be of a translucent character and nodules in the iris may be found. If the course of the uveitis is unfavourable, posterior synechiae may cause great irregularity of the pupillary margins, and fibrotic changes in the anterior chamber may lead to glaucoma and cataracts.

The uveitis due to sarcoidosis is not recognizable from local appearances alone, and other signs such as BHL or lung infiltration especially if associated with low tuberculin sensitivity must be sought before the diagnosis can be made.

A syndrome of fever, bilateral parotitis and uveitis known as uveoparotid fever or Heerfordt's syndrome is occasionally seen in sarcoidosis. It follows a protracted course with prolonged low grade fever and localization of sarcoid tubercles in the parotid, sublingual and submaxillary glands and in the uveal tract. Bilateral facial nerve palsy may be associated with the parotid disease.

The prognosis of sarcoid uveitis is generally favourable, especially if treated early with local steroids. If anterior uveitis is severe systemic steroids may have to be used.

Keratoconjunctivitis sicca of the type seen in Sjogren's syndrome due to a deficiency of lacrimal secretions is associated with involvement of the lacrimal gland. It presents as dry, sore, red eyes and there is often degeneration of the epithelial cells of cornea and conjunctiva. Small follicles of typical sarcoid histology have also been described in the conjunctivae. Also, the hypercalcemia that occurs in some cases of sarcoidosis can give rise to deposits of calcium salts in the cornea or conjunctiva.

LIVER

Next to the lymph nodes and lungs, the liver shows the greatest frequency of involvement in sarcoidosis. While biopsy results show the liver to be involved in about 65% of cases, clinical evidence of liver involvement is found in a much smaller proportion of patients.

Asymptomatic hepatomegaly is common as are mild elevations of serum bilirubin and alkaline phosphatase. Serious manifestations of liver disease such as jaundice and portal hypertension have been described. However in view of the rarity of these findings in sarcoidosis it is not possible to be certain whether such factors as viral hepatitis, alcoholism, and malnutrition may have played a part in at least some of the reported cases.

The hyperglobulinemia which occurs in some cases of sarcoidosis is not correlated with the presence of tubercles in the liver.

SPLEEN

Scadding reports a palpable spleen in approximately 10% of his patients, although in less than 1% of his series was it a presenting sign. Involvement of the spleen without splenomegaly is present in a larger number of patients. Very large spleens and spontaneous rupture of spleens infiltrated with sarcoid tubercles have been described.

Among the symptoms attributed to sarcoidosis of the spleen are local pain, discomfort, anorexia and vomiting.

In most cases of sarcoidosis the blood count is within normal limits. There have been a few reports of hemolytic anemia and pancytopenia associated with splenomegaly, but generally erythropoiesis is unaffected.

KIDNEYS

The kidneys are among the organs less frequently reported at autopsy to be invaded by granulomas of sarcoidosis.

Renal insufficiency in sarcoidosis may result from (a) widespread granulomatous infiltration of the kidneys; and/or (b) nephrocalcinosis with or without calculi secondary to hypercalcemia and hypercalcuria. Of the two causes of renal insufficiency in sarcoidosis, the latter is the more common.

BONES AND JOINTS

The incidence of involvement of distal phalanges of the hands and feet varies from 20% to less than 5%. The osseaus lesions are of two types; cystic lesions of hands and feet which are often associated with overlying skin changes and are asymptomatic and visible as punched out lesions on x-ray; and diffuse manifestations with thinning of the cortex and reductions in the number of bony trabeculae may also occur.

Sarcoid foci have been reported in almost every bone, including those of the skull and vertebrae, but are of diagnostic value only in the hands and feet.

The most frequent form of involvement of the joints in sarcoidosis is the febrile arthralgia, which may occur in the early stage of BHL often accompanied by erythema nodosum. Usually the larger joints especially ankles, knees, wrists, and elbows are most often involved clinically, and the symptoms are transient. In other cases the arthritis may be chronic and biopsy of synovium will show non-caseating tubercles. Patients with chronic sarcoid arthritis may respond to colchicine. When the small bones of the hands and feet are severely affected the intervening joints frequently show periarticular swelling and tenderness.

MUSCLE

Symptomless infiltration of muscles is common, although clinically evident muscle involvement is rare. No consistent correlation between objective changes in muscle and the presence of symptoms has been observed. Symptoms of muscle involvement when this occurs however, vary from mild to very severe pain accompanied by stiffness.

Palpable nodules may develop in the muscle. Wasting occurs, especially in the proximal muscles of the shoulder and pelvic girdles, and in some cases it may be severe enough to simulate progressive muscular dystrophy. Muscle biopsy is likely to be positive in such patients.

GASTROINTESTINAL TRACT

Sarcoidosis with symptoms related to lesions of the gastrointestinal tract is rare. When it does occur, the most common site is the stomach where it is usually associated with achlorhydria. Radiographic findings have included antral narrowing and gastric ulcer.

ENDOCRINE

Involvement of endocrine glands in sarcoidosis is rare. Diabetes insipidus arising from infiltration of the posterior lobe of the pituitary or hypothalamus has been reported most frequently.

NERVOUS SYSTEM

Sarcoidosis may affect the nervous system in several ways. Among the cranial nerve palsies produced by sarcoidosis the facial is the most frequently involved. Characteristically it is a transient palsy of lower motor neurone type. Peripheral nerves may be affected by direct involvement of nerve sheaths or roots.

In the central nervous system sarcoidosis produces two sorts of changes; infiltration of the meninges especially at the base of the brain and more rarely in the spinal canal, and local deposits of sarcoid granuloma in the substance of the brain or spinal cord.

LABORATORY FINDINGS

Common laboratory findings are a mild anemia, leukopenia, eosinophilia, elevated sedimentation rate and rarely thrombocytopenia.

It is well established that in sarcoidosis there is a diminished reactivity to agents causing delayed tuberculin-type skin responses. This is typified by tuberculin anergy which is noted in about 85% of patients. In addition delayed skin reactions due to mumps virus, a Candida albicans antigen, a pertussis antigen, and trichophyton are less intense in patients with sarcoidosis. The depression in reactivity to delayed skin responses remains unexplained. Some investigators postulate that deficient production of the cell-born antibodies which underlie delayed skin reactions is responsible. Patients with sarcoidosis can become sensitized normally to agents producing immediate skin reactions, and evidence

suggests that they have a normal capacity for producing circulating antibodies in response to antigenic stimulation.

In active and extensive sarcoidosis, there is a rise in the total serum proteins, especially in the gamma-globulin fraction, associated with a rather low albumin. Large deviations from normal have been described only in patients with extensive active disease, while striking changes are not to be expected in patients with less extensive disease. The estimation of serum proteins will not be of diagnostic significance in a patient in whom the diagnosis is in doubt.

Hypercalcuria and hypercalcemia have been observed in as many as over one-third of patients with sarcoidosis. Calcium balance studies have generally shown that the hypercalcemia is associated with high urinary and low fecal calcium excretion and thus there appears to be an abnormally high absorption of ingested calcium from the gut. There is good evidence to suggest that the abnormal calcium metabolism is associated with abnormal sensitivity to vitamin D. This hypothesis is further supported by the fact that prednisone has been shown to prevent or reverse the action of vitamin D and that prednisone restores abnormally low fecal calcium values to normal and will control hypercalcemia in sarcoidosis. The inter-relations of serum, urine and fecal calcium in sarcoidosis are complex. The changes in serum, urine and fecal calcium are to a certain extent independently determined. Hypercalcemia and hypercalcuria have occurred in the absence of increased absorption of calcium by the gut and hypercalcuria has been found in patients with sarcoidosis despite normal levels of serum and fecal calcium.

These findings do not invalidate the hypothesis of increased sensitivity to vitamin D since it is now evident that vitamin D can augment urinary calcium independently of the level of serum calcium and that it can induce hypercalcemia by its action on bone before it stimulates increased absorption of calcium. The hypersensitivity to vitamin D, remains unexplained however. It has been suggested that affected sarcoid patients may be deficient in ability to inactivate vitamin D or that there may be a defect in tubular reabsorption of calcium.

Elevation of serum alkaline phosphatase level has been attributed to intrahepatic granulomas rather than bone lesions. Serum uric acid levels may be elevated even in the absence of renal insufficiency.

DIAGNOSIS

The diagnosis of sarcoidosis may be made on the basis of clinical evidence alone, but a biopsy is usually done to confirm the diagnosis. Absolute certainty of the diagnosis can only be achieved by autopsy or by multiple biopsies. However, a biopsy showing typical histological changes does not by itself justify the diagnosis of sarcoidosis in the absence of a clinical picture consistent with this disease.

When an apparently healthy person, or a patient with erythema nodosum or febrile arthralgia is found to have well circumscribed symmetrical enlargement of hilar nodes, the diagnosis of sarcoidosis is so likely that confirmation by biopsy is not required for practical management. If, on the other hand, there is doubt about the diagnosis, confirmatory histological evidence should be sought and the Kveim test done. Sources of biopsy material which have been employed are lymph nodes, liver, skin, lung, bronchial mucosa and conjunctiva. Liver biopsies reveal granulomas in 70 to 80 per cent of cases, even without clinical evidence of impaired hepatic function. Random biopsy of skeletal muscle in patients with fever and arthralgia shows sarcoid granulomas in a high proportion of cases.

The Kveim test is performed by the intradermal injection of a heat sterilized, phenol preserved suspension of human sarcoid tissue, usually spleen or lymph node. In 50 to 80 per cent of patients with other evidence of sarcoidosis, a small dull red papule appears within 2 or 3 weeks, which continues to increase in size up to 8 weeks and then subsides.

Positive tests are more frequent and more intense in the early active stage of the disease. The specificity of the reaction can only be confirmed by biopsy, usually performed at 4 to 6 weeks after injection. The biopsy typically shows well formed, non-caseating epithelioid cell tubercles.

There is evidence that BCG vaccination may cause some individuals to become weakly reactive to the Kveim test. A variety of granulomatous and collagen vascular diseases can give false positives, but these occur in only 2 to 5 per cent of the tests. However, many false negatives are reported in patients later shown to have the disease.

Laboratory data, as indicated previously, will lend support to the diagnosis.

TREATMENT

Relatively asymptomatic patients require no treatment. The only therapeutic agents with a predictable beneficial effect in sarcoidosis are the corticosteroids and ACTH. Their effect is to suppress the active phase of the sarcoid granuloma and provide symptomatic relief. Indications for treatment are (1) ocular changes not responding to local treatment, especially posterior uveitis (2) hypercalcemia (3) disfiguring skin lesions (4) progressive pulmonary infiltration with significant functional impairment (5) central nervous system involvement with significant functional impairment (6) involvement of a vital organ.

Prednisone is administered in an initial daily dose of 30 to 40 mgms. This dose level is maintained until either a satisfactory response has been observed, generally within 1 to 2 weeks, or it becomes evident that the symptoms are unlikely to be controlled. If there is a satisfac-

tory response the dose should be reduced gradually until the minimum maintenance dose which controls symptoms has been found. Therapy should be continued for 6 months or longer with periodic attempts to reduce dosage. Maintenance therapy for many years may be necessary. Problems in long term therapy include endocrine side effects and increased susceptibility to fungal infection.

The anti-malarial drugs, especially chloroquine have been observed to induce improvement in skin lesions over periods of several weeks, but relapse is the rule when these drugs are withdrawn. Improvements in a few cases of pulmonary infiltration have been observed with chloroquine but its beneficial effects here are less certain than in the treatment of skin lesions.

Alternative methods of treatment such as administration of vitamin D, colchicine, cytotoxic drugs, antituberculous drugs and radiotherapy have been employed and found to be ineffective.

PROGNOSIS

The mortality rate in sarcoidosis has been reported to be from 5 to 28 per cent. Although renal failure from hypercalcemic nephropathy and heart involvement are very occasional causes of death in sarcoidosis, the principal cause is pulmonary fibrosis leading to respiratory insufficiency with or without right ventricular failure.

The feature most closely associated with progressive and fatal sarcoidosis appears to be cutaneous involvement, and the less favourable outcome in Negroes may be related more to the greater frequency of skin lesions in this group than to any other racial differences. The difference in prognosis between patients with and without cutaneous disease exists regardless of race and other system involvement.

Recurrence of sarcoidosis after complete clearing is rare.

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SUN LIFE OF CANADA

General Practice: Theoretical v.s. Practical Medicine

Mel Iscove 6T9

INTRODUCTION

The purpose of this short paper is to present in an organized manner some of my observations during a summer experience in the General Practice Clinic at Toronto General Hospital. This position was unique in that it provided an opportunity for participation in clinical medicine on a graduate level, for a student still enmeshed in the undergraduate training program. This type of experience allows an unusual double perspective: the basically theoretical, biologically-oriented approach of the medical student makes a sharp contrast with the practical, often psychologically-oriented dealings of the practising physician, and the differences must be reconciled in order to produce a "realistic" orientation.

My first and major discovery was that general practice in a busy (i.e. average) out-patient department or private office is far from a strict application of text-book diagnostic and therapeutic techniques. These, as learned in medical school, tend to apply to an ideal situation: the physician knows all of medicine, the patient is intelligent and capable of providing a reasonable history under proper guidance, all the time and money in the world is available for physical examination and special investigation, the patient fully understands his problem as explained to him, and follows completely the treatment course prescribed. The barriers to the realization of this ideal situation present themselves at every stage of the above resumé.

Assuming that the physician is competent and has attained a reasonable awareness, if not thorough knowledge, of the major manifestations of disease, the problems reduce themselves to:

1. The problem of diagnosis
2. The problem of investigation
3. The problem of treatment
4. The problem of the patient's behavior

Before dealing with these problems specifically, I think it fitting to answer a frequently posed question: "Who are the patients attending a G.P. clinic, and what sort of diseases do G.P.'s deal with?

In the G.P. clinic at T.G.H. a great many of the patients are people who have no family doctor, either because they have just arrived in Canada, just arrived in Toronto, never went to a doctor before in their lives, or feel that a G.P. at a hospital knows more than a G.P. practising in the periphery. These are the people who come with no referral.

Of those who are referred, a large number are referred from Emergency for follow-up after initial treatment there. Others are referred from specialty clinics, which require that their new patients be given a complete general examination by a G.P. before the specialist examination. Still others are referred from the wards for follow-up after a period of hospitalization for an acute illness.

Finally, the patients may be divided into two groups on a financial basis: the paying and the non-paying patients. The latter group are those with no insurance, either due to recent arrival in Canada, ignorance, fear or just stubborn refusal to fill out an Omsip card.

In terms of diseases, the G.P. deals with the two main types: acute and chronic. The chronic problems involve mainly geriatrics — the diseases of aging, resulting from altered physiology with superimposed pathology; chronic dermatological problems; gastro-intestinal problems; and the arthritides. Acute problems demand a great deal of G.P. time, and consist of anything that anybody may observe in themselves in terms of altered or impaired function throughout the body.

1. THE PROBLEM OF DIAGNOSIS

Turning now to the four problems listed above, it may be seen that the problem of diagnosis becomes first of all the problem of eliciting a clear history in a minimum of time. Once this is achieved, the next challenge presents itself: how significant are the symptoms — do they add up to a unified picture of a specific pathological process, or do they contain inherent contradictions? In other words: do these symptoms suggest organic disease? The possibility that the symptoms are a functional reflection of a temporary upset must always be carefully considered. To illustrate this problem I have chosen a fairly typical case: a young man in his late twenties, born in Greece and emigrating to Canada via Germany, came to the clinic complaining of frequent diarrhea-like bowel movements, associated with a sensation of "gas shifting" in the abdomen. On physical examination there were no unusual findings (some abdominal tenderness). Rectal examination was negative for occult blood. Still, in compiling a differential diagnosis, the first distinct disease entity that came to mind was ulcerative colitis. This is a disease that presents in a multitude of ways, ranging from a smoldering proctitis to an acute fulminating colitis involving the entire large bowel. As I began to discuss my differential with the staff doctor assigned to this case, he interrupted me with this comment: "You cer-

tainly know the mechanisms of disease and the principles of history-taking, physical examination, and treatment. But when it comes to differential diagnosis you have your priorities backwards. *You* think of ulcerative colitis first, whereas *I* have to remind myself that U.C. is even a possibility." In fact, he said that in eight years of practice he had never run across a case of ulcerative colitis.

It could well be that this patient was an example of a syndrome seen often in recent immigrants, which might be called the syndrome of the "isolated immigrant terrified by the threat of disease". I saw such an immigrant recently — a young East European male of twenty — who came to clinic complaining of tongue discoloration and indigestion. He knew he had had hepatitis as a youngster and he feared that his liver was affected once again, the disease manifesting itself in his tongue. After ruling out an element of malnutrition, and advising him to include fresh fruit and vegetables in his diet, I consulted the supervising physician, since I was at a loss to explain the symptoms. (The tongue appeared perfectly normal on inspection.) It was the supervising doctor who mentioned the above syndrome: he explained that many immigrants who are without friends or relatives in Canada become terrified when they realize that, should they become ill, they have nobody to look after them, and furthermore their source of income may be lost. Immediately they become tense and preoccupied with their health; they seize upon minor symptoms, usually gastrointestinal, and exaggerate them; this aggravates and perpetuates their fear, and when they consult a physician they are in a real state of agitation. He then went in to speak to my patient; in several minutes he was down to the essentials of the situation, confronted with a high-strung, anxious individual who indeed had no family or friends in Toronto, who was lonely, and depended on his health for continuing his work as an electrical engineer. He had apparently converted all his fear about his social adjustment into a fear that he was getting a recurrence of hepatitis, and he was quite grateful when the doctor told him that his problem was *not* his tongue, that he was running away from a necessary social adjustment, and that he would have to exert himself to make friends and establish healthy outlets for his intellectual energy.

A similar problem involves the wives of immigrants. These women come to the physician and give their story through an interpreter (often the husband). The story is one of G.I. complaints: vague epigastric discomfort, feeling of pressure in the throat, cramps, headache, dizziness (= light-headedness), all of which are often worse in the morning. Needless to say, examination reveals nothing, as does upper GI series, gall bladder series, ENT consultation, etc. However, if one questions these women specifically regarding their adjustment to life in Canada (do they like living here? Do they have many friends? Do they go out socially? Do they miss their old country) the response is very emotional indeed. I have seen two patients within three days — one from Italy, one from Japan — burst into tears when asked if they were homesick. The Japanese woman as well knew no English, was confined at home with her children, and felt isolated and alienated in a strange society. The Italian woman, living in the Italian community, was attempting to raise a family of seven (ranging from 7 to 21 years) according to old-country standards, and discovering that the outside forces of North-American culture, with which she had no ties, were challenging her control over her English-speaking brood. This she found very distressing.

Without attempting to deduce the interconnections between such adjustment problems and the presenting symptom-complexes, I think one may safely accept the proposition that such a state of inner turmoil can and does affect the individual's balance of health. This type of emotional turmoil must be searched for as a contributing factor, perhaps even the main factor, producing the bizarre symptom-complexes presented to us for evaluation by recent immigrants.

2. THE PROBLEM OF INVESTIGATION

Where the diagnosis of an organic disturbance is readily reached clinically, the investigation serves two obvious purposes: to confirm the diagnosis objectively, and to quantitate the disease. When the initial diagnosis is truly provisional and/or based on the impression that the problem is functional, the physician often orders laboratory tests just to assure himself that an organic problem has not been overlooked. The general tests most commonly ordered are: complete blood work (Hbg, W.B.C., sed. rate, smear and differential); B.U.N. and blood sugar; urinalysis and urine microscope (routine for all new patients). In most cases these tests confirm the clinical impression that there is *no organic disease*. This occurs roughly in seven cases out of ten.

Occasionally, though, a very high sed. rate or a peculiar differential count point toward organicity and suggest that further investigation is in order. Quite often a blood sugar of 250, 350, or even 450 will be discovered in a patient whose clinical status provided no hint of diabetes mellitus. One very bizarre example of such findings is the case of a lady in her early seventies who complained of nothing but a metallic taste in her mouth of several months duration. Previous history of hemorrhoids somehow led to a barium enema being done (to rule out GI bleeding as the source of an incidental anemia); the x-rays revealed a huge eroding carcinoma of the ascending colon. Thus these broad screening procedures have a clear value as indices of organicity, and may establish a surprise diagnosis.

Just as often, though, the opposite occurs. A seemingly *organic* disease will be *unmasked as functional* by negative lab. results. Normal blood work, normal GI series very often change a diagnosis of peptic ulcer to a diagnosis of "functional dyspepsia".

The preceding two examples may be gauged roughly to represent two cases out of ten. The remaining case in ten is straightforward: a diagnosis of *organic* disease is *confirmed* by special investigation (e.g. peptic ulcer confirmed by upper GI series).

The more specialized investigations (blood enzyme levels, endocrine studies, ECG, EEG, etc.) are not ordered too hastily on out-patients unless the case happens to be the one case in ten which is unequivocally organic. Because of the high percentage of functional disturbance, it is impractical to do elaborate investigations routinely. As one G.P. put it: "Are you going to order skull films, EEG, echogram and carotid arteriography on every patient complaining of longstanding headache? This is lazy medical practice — there is a great deal you can do yourself to diagnose the problem. You can take a more careful history, examine the fundi, transilluminate sinuses, check the ears, etc. Since the headache is most likely functional, fancy tests waste the patient's time and money, without clarifying anything."

Thus, the indiscriminate ordering of a full battery of tests is just not done by G.P.'s. Perhaps it is for this reason that the experienced G.P. comes to rely on clinical skills, especially in history-taking, and on a sixth sense, a "nose for sniffing out which problems are serious."

The factor of needless expense is an important consideration here as well. Certain blood studies are extremely expensive, and the question arises: is it worth thirty dollars to this patient to be reassured by one more lab tests that his problem has no organic basis? Or, does this patient have thirty dollars to spend on such reassurance? Many patients simply haven't the money and are not covered by insurance. To quote figures from an American report[1]:

"80% of the population carry some form of pre-paid health insurance. Most of this is intended to pay for hospitalization, but more than 90 percent of the insured also carry surgical insurance and 30 percent are insured for major medical costs." We may estimate that the figures, particularly the last one, would be the same or higher in Ontario. All in all, this still adds up to a substantial proportion of the population who are uninsured — i.e., who pay the full cost, or can't pay any of it. If the doctor orders costly tests for these people *without a solid indication* he may be embarrassed to find his generosity called upon to finance them.

We are not considering those cases in which the test is essential to the diagnosis; that is another matter entirely.

3. THE PROBLEM OF TREATMENT

Since the G.P. diagnoses a wide range of conditions, he must be prepared to employ an equally wide range of treatment programs. At the same time the G.P. does not hesitate to call in a consultant or refer the patient when it becomes apparent to him that more specialized, more detailed knowledge and skills are required in the case.

Again, a great deal of judgment must be exercised in adapting the treatment to the patient as well as to the disease, bearing in mind the constant *threat of iatrogenic illness*. This hazard often leads to the non-treatment of some treatable diseases. For instance, I saw one 75-year-old woman who had mild hypertension, for which she had been receiving Hygroton tablets from her physician. She complained of light-headedness and occipital throbbing sensations. In view of her history of a previous cerebral thrombosis, we elected *not* to switch her to a different anti-hypertensive drug, since it might cause orthostatic hypotension and further decrease an already impaired cerebral blood flow. It was deemed safer to leave her with her present symptoms rather than risk making matters worse. This type of problem arises often in the treatment of elderly patients.

In younger patients it is the *functional disturbances* that predominate in the clinic, as they do in private practice. These are treated mostly by reassurance or other forms of superficial psychotherapy: taking a detailed family and personal history, encouraging the patient to "ventilate" his problem, offering a certain amount of support.

For the *chronically ill patients* coming to the clinic, whether their problem is physical or psychological, the treatment aim is to restore as much function as possible. If the patient has a number of problems, the attaining of this goal may take all of his time. Thus, one G.P. introduced me to an old patient of his in his early fifties, who was badly crippled with longstanding rheumatoid arthritis; he had recently concluded a long stay in Weston Sanitorium for T.B., and prior to that had been an alcoholic. When asked how he spends his time now, he cheerfully recited his timetable: every morning was taken up by a hospital visit, either for physiotherapy, arthritic clinic, or surgery clinic, with the occasional visit to G.P. clinic. He has had numerous operations on his hands, and on his feet, to correct arthritic deformities; he now manages to dress himself without help. In this case the battle to restore function was won, but maintaining this function is a full-time job.

This example leads to another point regarding treatment: the G.P. must have some knowledge of the existing institutions to which patients may be sent for rehabilitation (or even just for shelter). In the hospital O.P.D. clinics there are social workers for assistance with these matters, but in private practice the physician must look after these areas himself. Toronto Rehabilitation Centre and Riverdale Hospital are two examples of local institutions a busy G.P. will often enlist for the treatment of his chronic patients.

4. THE PROBLEM OF THE PATIENT'S BEHAVIOR

This brings us to the last area which presents obstacles to attaining an ideal situation in medicine: the problem of the patient's reactions to our efforts. Reduced to its

essentials the main problem here is lack of cooperation, deliberate or otherwise.

This may occur during the history-taking, with those patients for whom each question serves as a catalyst to release a flood of reminiscences of previous symptoms, and who would rather reveal their entire life-history than answer the question. These people may be considered naive: they miss the point of our functional enquiry altogether, and have to be gently guided back to the issue under discussion. At times a language barrier is added to the naiveté: thus, when I asked a Hungarian man who has been in Canada over ten years, "How long does your pain last?", he replied confidently, "Last? — Oh, last Friday!"

More often lack of cooperation is a hindrance to our treatment efforts. This is something the G.P. meets every day, whether in the obese patient with hypertension who will not stick to her 1200 calorie diet, or in the cardiac patient who continues to smoke two packs a day yet wants the physician to remove his chest pain. An extreme example of negative reactions to medical treatment is found in a recent article on long-range hemodialysis for chronic renal failure:[2]

"Two reports in particular emphasize the high incidence of emotional disorders associated with chronic hemodialysis. Some . . . were of a magnitude to cause discontinuation of the dialysis due to poor cooperation or requests by the patient to terminate treatment, thereby bringing about the patient's death . . . At a recent conference held by the National Dialysis Committee there were at least seven reports of patients going on "suicide binges" during which they would break all dietary restrictions, consume large quantities of food and drink, come to the hospital in a coma, and die."

They quote the case of one patient whose "illness began when he was seventeen . . . diagnosed as glomerulonephritis. At that time he was placed on a diet but did not follow it as he 'felt so well' after a few months. However he was warned that a second episode of nephritis might 'kill' him." Eight years later he was an electrician's apprentice, married, with a child, and had chronic glomerulonephritis. When told he had been accepted for hemodialysis, he reacted strangely: "he wasn't so sure at all if he wanted to go on this machine. He thought he'd just go home and 'live it up' and save the machine for someone who needed it more . . . he didn't want to be dependent on government money to support his existence . . . he may not be around that long . . . he might just go home and jump out a window."

As he began to cooperate more he had "an 'accident' involving his stepping out of a boat one weekend . . . soaking his cannulae (inserted in his leg) and subsequently causing the shunt to become infected."

An attempt to explain these adverse reactions is not within the scope of this article. It is enough to recognize that patients may have conflicts which *hinder* them from following advice given in their best interest, even when their lives are at stake.

One feature of the above case deserves further comment, as it is familiar enough to all G.P.'s; this is the fact that patients tend to discontinue treatment programs when they feel better (in this case the *diet* was dropped). The reluctance of patients to take medicines or visit the doctor when asymptomatic is a great impediment to necessary treatments; it often interferes with 10-day penicillin therapy for strep. prophyllaxis in pharyngitis, for example. While oral penicillin is easier to take, patients will stop after three days when the throat is better; thus injections are resorted to, to ensure that the patient gets the full dose. The same problem arises with diabetics who become careless about testing their urine and regulating their diet.

Yet another problem in cooperation arises with those patients who are unwilling to go even as far as the average G.P. in recognizing the connection between psyche and soma. These patients insist that they have come to us for treatment of a back, a stomach, a throat, and give strict orders to "leave my home life out of it". One such patient returned to the clinic week after week, complaining of excruciating pain in all joints on movement (back, shoulders, neck, hips, knees). Each week the pains were worse and the impairment of function greater; yet physical examination, X-rays, and blood studies failed to implicate any of the organic diseases in our differential diagnosis. The pains appeared to be truly psychogenic; arthritic clinic confirmed our impression too. At this point a careful personal history was taken: she has been married for twelve years to a "good-looking brute" who tyrannizes her, forces her to scrub floors until they are spotless, and has often beaten her, although he is always sorry afterwards. She was not prepared to consider the pattern of this marriage as pathological, nor was she interested in seeking a divorce. She refused to consider any connection between her marriage and her pains, either with us or with a specialist when we suggested that. Recently, she stopped attending the clinic; no doubt she has started the whole slate of investigations under some other physician.

PATIENT'S BEHAVIOR CAUSING DUPLICATION OF EFFORT

This leads to another problem relating to G.P.'s, which I would like to mention here: the problem of the "shortage of doctors". Due to the phenomenon of Doctor-shopping, as practised by the last patient and many of her confreres of both sexes, a moderate shortage of doctors may appear greatly magnified. When we consider how much time each doctor must spend with this woman, often unaware that she has been seen elsewhere (because she is too ashamed to admit it), we see how her uncoordinated visits to five doctors may appear in each

doctor's statistics, as if five different patients were treated. Yet it is only one patient, and an uncured patient at that, who may see a sixth, seventh, and "n"th doctor before finally giving up. Add to this the large number of patients who keep trying different doctors until they find the one whose personality appeals to them, and it is easy to imagine the amount of overlapping that occurs in medical services. One G.P. estimated that only five percent of his new patients complain of a doctor-shortage in Toronto. Another, without meaning to imply anything about his personal popularity, estimates that one-third of his new patients fail to return after one or two visits. These are undoubtedly the "shoppers". Turning out more doctors from medical school is certainly a roundabout way of handling this problem.

PHYSICIAN'S BEHAVIOR CAUSING DUPLICATION OF EFFORT

While the patient is responsible for much of this needless duplication that slows down our service, physicians themselves are to blame in the area of referrals. According to a recent American report[1]:

"When a patient is referred from one physician to another, for example, tests and procedures may be repeated because the second physician is uncertain about the previous tests or because he is entirely unaware that they were made.

"A more serious problem is the failure to transmit prior medical information when a patient is transferred from one physician to another. This not only necessitates duplicate testing, but often deprives the new physician of information that may be crucial to reaching the proper diagnosis. The extent of the deficiencies in information transferral is indicated by a study of referrals to a university hospital. In only 40 percent of the cases did the referring physicians provide any medical information on the patients."

INEFFICIENCY : AN INAPPROPRIATE LUXURY

If these two areas of duplication could be eliminated, medical service would be a great deal more efficient. Toward this end the American report concluded that "current technologies in data processing are sufficiently advanced so that centralized banks of patient data might be established. These banks would accumulate individual medical records and make them promptly accessible to authorized physicians at the point of care." Such a system could well eliminate much of both types of duplication outlined above, and is worth considering in Canada, too. This brings us to the conclusion of this study. The purpose of this paper has been not to advise or to criticize, but rather to record certain observations. With the exception of a small digression at the end I have attempted to follow my original outline. The problems and paradoxes of general practice are many; I do not pretend to have touched on all of them, but at least I hope to have demonstrated some of the surprises which await the medical student when he leaves his study and enters his office. From my own experience, the opportunity of being an "outsider" temporarily on the "inside" of real practice would seem to be invaluable in the preparation of the complete physician.

ACKNOWLEDGEMENT

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Nephrotoxicity With Chronic Phenacetin Abuse

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Nephrotoxicity secondary to chronic abuse of phenacetin-containing analgesics was first described in Europe, in 1953 and has since been extensively reported throughout the world. The purpose of this article is to reveal some of the hazards which may be associated with chronic abuse of these drugs.

Phenacetin is most commonly sold in combined preparations with acetosalicylic acid, caffeine and codeine (APC-C). One very dangerous feature of these preparations is that they are commonly sold in tablet form as proprietary drugs, and are not controlled by prescription. Certain countries now limit their use to prescribed forms, and in Europe legislation is being considered to control their usage. They are used as mild analgesics for headache, arthritis and "non-specific" pain and their chronic abuse is often associated with some personality disorders.

Although phenacetin is the active ingredient in these preparations, one of its metabolic products, acetaminophen, is also marketed as an analgesic drug. The pharmacological actions of both are antipyretic and analgesic. They will relieve voluntary muscle pain of marked intensity but not that associated with hollow viscera or smooth muscle spasm. The drug is totally absorbed in the gastro-intestinal system, conjugated in the liver, and excreted in the kidney. A small amount is deacylated to an unidentified product which is known to oxidize hemoglobin to methemoglobin.

FORMS OF ABUSE

Phenacetin abuse has been considered as both acute and chronic. Acute toxicity has been reported in doses of up to 5 grams and is associated with cyanosis secondary to methemoglobinemia.

Chronic toxicity, the more common problem, has been associated with nephrotoxicity, anemia with methemoglobinemia and sulfhemoglobinemia, peptic ulcerations, and personality disorders. One may suspect the effects of chronic abuse in anyone ingesting more than 5 tablets per day for periods of 3 years or more. Some have related toxic effects to a total intake of 1 kg. Frequently patients take as many as 40 tablets per day.

Gault et al, in a careful analysis of 500 consecutive patients admitted to a Veterans' Hospital, revealed that 110 took APC-C tablets regularly. Of these, 13 had consumed more than 5 kg. of phenacetin. He further demonstrated histological and pyelographic evidence of kidney damage in these patients, four of whom had consumed over 14 kg of phenacetin.

NEPHROTOXICITY

The most commonly reported toxic effect of phenacetin is its nephrotoxicity. Biopsy, autopsy, and pyelographic studies have revealed that this nephrotoxicity consists of papillary necrosis, and chronic interstitial nephritis.

Despite considerable degrees of renal damage, symptoms and signs are generally absent. Hypertension is the most commonly reported sign, although even this is seen in a minority of patients. Some patients with a history of phenacetin intake have presented in terminal renal failure, with all the signs and symptoms of uremia.

Urinalysis may show trace to 1+ proteinuria, and possibly a decreased specific gravity. The urinary sediment may show a few red blood cells, and Rappoport et al have described the presence of enlarged and granular white blood cells. In some patients with papillary necrosis, fragments of renal papillae may be seen. The presence of these is usually associated with renal colic or symptoms of bladder irritation.

Reports vary on the extent to which biochemical parameters of renal failure are impaired. The earliest change is a decreased concentrating ability. It is generally concluded that a creatinine clearance of less than 50 ml per minute is definitely indicative of renal disease.

Diagnosis is best made on the basis of intravenous pyelography or biopsy. High dosage urography with tomography may show evidence of papillary necrosis.

ANEMIA

Most patients develop a mild to moderate degree of anemia; however, the hemoglobin may be as low as 6 gm%. This is usually a normochromic normocytic type of anemia. Evidence of a hemolytic process may frequently be seen in the form of Heinz bodies and reticulocytes.

Methemoglobinemia and sulfhemoglobinemia are more specific findings, the latter being seen in quantities of up to 13 gm%. Both types of these hemoglobinopathies may present as cyanosis. This cyanosis is unrelated to either cardiac or respiratory disease and is due to the presence of excess reduced hemoglobin in the blood. Patients have often presented with anemia as their primary abnormality.

PEPTIC ULCERATIONS

Gastric ulcerations are particularly frequent among abusers of these mixed analgesics. Some evidence sug-

gests that the acetosalicylic acid in these agents is the most likely etiological agent. The association of salicylates with damage to gastric mucosa, ulcerations and hemorrhage is well known. Caffeine has also been suggested as a possible causative factor in gastrointestinal bleeding. Frequently, patients with gastrectomies have been noted to eventually present with renal damage. Although the precise agent is uncertain in patients who abuse the analgesics and have gastrointestinal complaints, these preparations must be considered as a possible etiology.

PATHOGENESIS

The pathogenesis of the toxic effects of these drugs is unknown. Many explanations have been offered by different investigators. However, attempts to reproduce any of these toxic effects in animals have been unsuccessful.

The anemia has been explained by several possible mechanisms: a glucose-6-phosphatase deficiency related to phenacetin, an antigen-antibody reaction causing hemolysis, or direct damage to the red blood cell. None of these hypotheses has been definitely proven.

More than one mechanism has been postulated to explain the renal damage. Certain investigators have implicated a contaminant, 4-nitro-chlorbenzol, as a possible factor in renal damage. Zollinger postulated that deposition of phenacetin or its metabolic products in the kidney tubules was the mechanism of injury. Mozler stated that chronic hypoxia to the kidney, secondary to methemoglobinemia and sulfhemoglobinemia, was the major factor. A recent explanation is that of a development of hypersensitivity to phenacetin or one of its products. Still others have explained the changes on the basis of an increased incidence of infection. It is apparent that further investigation is required to fully clarify the pathogenetic mechanisms.

DISCUSSION

Abuse of these combined analgesics and their effects on the kidney and the hematological system has been the subject of over 1,000 reports since 1953, when they were first described by Zollinger. Most initial reports were in Central Europe, but more recently cases have been reported throughout Australia, Great Britain, and North America.

Gault et al, in a recently published survey, considered that they were dealing with a syndrome consisting of: a history of psychiatric disorder or headache, with recent manifestations of gastrointestinal disease and anemia, coupled with evidence of renal impairment. He emphasizes consideration of the syndrome at an early stage so that later manifestations, often fatal, may be prevented.

The prognosis of this condition is still not well established; however, Kasanen has shown that by stopping the intake of phenacetin, some spontaneous improvement of kidney function is seen. He has related prognosis to serum creatine level on admission, and shown that some patients admitted to hospital in severe renal failure died in hospital, while 22% (of 130 patients) died within 4 years. Only 25% of those with a serum creatine of more than 5 mg% on discharge survived.

SUMMARY

Chronic abuse of mixed analgesics containing phenacetin has been reviewed as a cause of renal insufficiency associated with gastrointestinal ulcerations, anemia, and psychiatric disorders. Since consumption is largely in the form of proprietary drugs, the physician must ask the patient specifically about the use of any non-prescribed medications. Prevention of fatal disease is based on cessation of intake and education of the public regarding the dangers inherent in abuse of these drugs.

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The Syndrome Of Secretion Of Inappropriate Antidiuretic Hormone

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Introduction

In 1957 Schwartz and his associates documented two cases in the Am. J. Med.[6] The first case was that of a sixty-year-old hat cleaner who presented with hemoptysis and weight loss and was diagnosed on biopsy as having an anaplastic carcinoma of the bronchus. Peculiar electrolyte abnormalities were found on routine testing of blood and urine. The second case was that of a fifty-six year old prize-fighter who presented with anorexia, weakness and fatigue. Hyponatremia was found on admission. His condition worsened as he became dysphasic and disoriented. Burr holes revealed a normal CSF pressure. Hemiplegia and coma ensued prior to death, which was attributed at autopsy to hemorrhage from a duodenal ulcer. Also found was an anaplastic bronchogenic carcinoma.

Both patients exhibited normal renal and adrenal function as judged from clinical and biochemical evidence. Both showed continuous urinary sodium loss without corresponding losses of water or body weight. The urine remained continuously hypertonic to plasma and only transient elevations of serum sodium could be produced by a large load of a hypertonic saline solution. Fluid restriction led to sodium retention and a return of serum sodium to normal; however, restoration of liberal fluid intake re-established the sodium losing syndrome. Previously, Leaf et al[5] demonstrated that administration of long-acting Pitressin in Man was followed by water retention, weight gain, increased naturesis and hyponatremia. Hence, Schwartz et al postulated that the two patients presented a syndrome which was the result of inappropriate secretion of ADH-"inappropriate" because ordinarily when serum osmolality is low, the urine formed is hypotonic, reflecting a diminished ADH secretion and hence increased secretion of free water in an attempt to return the serum to normal osmolality.

The Salient Features of this Syndrome may be Summarized as Follows:

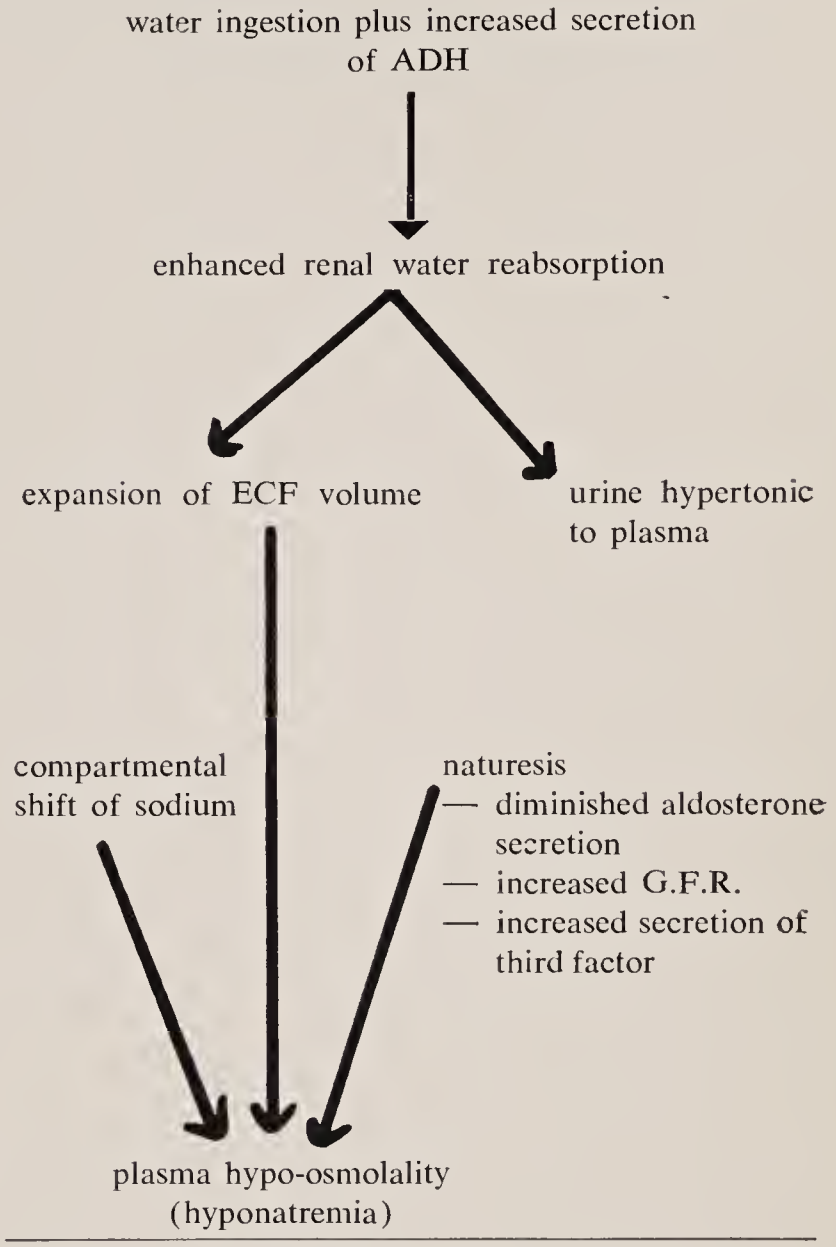
1) hyponatremia and consequent hypo-osmolality of the serum
2) continued renal secretion of sodium in spite of hyponatremia
3) urine that is hyperosmolar to the serum
4) clinical signs of normal or increased hydration, i.e. skin turgor and blood pressure are normal
5) normal renal and adrenal function

Pathophysiology

The pathogenesis of the syndrome of inappropriate secretion of ADH is represented in figure 1.

A logical explanation is that excessive ADH plus ingestion of water leads to excessive retention of water, expanding the extra cellular fluid volume and diluting the body fluids. This expanded ECF volume not only suppresses aldosterone (sodium retaining) secretion but also allows for increased G.F.R. and an increased filtered load of sodium. As well, the third factor, a postulated hormone of currently unknown origin, is elaborated at times of ECF surfeit and is thought to be responsible for the diminution of proximal tubular sodium reabsorption known to occur at such times. Since aldosterone secretion and excretion rates are normal and *not* depressed, and since the G.F.R. is *not* markedly increased, the "third factor" effect is probably the more important in producing the sodium diuresis. Kaye[4], who was unable to explain the serum sodium level entirely upon the previous factors, suggested that in response to slow retention of water and resultant intracellular hypotonicity, sodium shifts from the extracellular space to the intracellular, this influx being facilitated by the known effects of vasopressin on the cell membrane permeability.

FIG. 1
PATHOPHYSIOLOGY OF THE SYNDROME OF INAPPROPRIATE SECRETION OF ADH[7]


water ingestion plus increased secretion of ADH
enhanced renal water reabsorption
expansion of ECF volume
urine hypertonic to plasma
compartmental shift of sodium
naturesis
— diminished aldosterone secretion
— increased G.F.R.
— increased secretion of third factor
plasma hypo-osmolality (hyponatremia)

Symptomatology

The retained water is distributed over the whole of the body fluids, two-thirds intracellularly and one-third extracellularly. Symptoms are thus due to cellular overhydration and hypotonicity, that is, water intoxication.

There is considerable individual variation in the degree of hypotonicity which will produce symptoms. However, although the serum sodium concentration will fluctuate, depending on sodium and water intake during a given period, serum sodium concentration of 120 meq./1. or greater is usually asymptomatic, while one of 110 meq./1. or lower is accompanied by severe symptoms and neurologic signs of, for example: absent deep tendon reflexes, muscular weakness, Babinski response, bulbar or pseudobulbar palsy and hyperventilation.

The symptomatology is generally non-specific, but may mimic space occupying intracranial lesions or a diffuse intracerebral process. Neurologic consultation and surgical neurologic investigative procedures have, not infrequently, been associated with this disturbance. Mental confusion, fatigue, nausea and vomiting, headache, and anorexia may progress to the later manifestations of hostile and sometimes violent behaviour, episodes of coma with convulsions. Because of the general nature and insidious onset of the symptoms they are commonly attributed to other causes.

Clinical Signs

The signs of water intoxication are the reverse of those of sodium depletion, ironically, the disorder it is usually mistaken for. There are no signs of dehydration, but rather normal tissue turgor, elasticity, colour, temperature, blood pressure and pulse. Weight gain, as opposed to weight loss, is the rule. These signs are commonly accompanied by muscle weakness and sweating.

The Laboratory Findings

These reflect the increased ECF volume in the apparently depressed serum constituent readings.

Etiology of SIADH

The etiology of water intoxication is not necessarily related to SIADH. Surgical patients are especially vulnerable to water intoxication because of the anuria or oliguria for 12 - 36 hours which frequently follows surgical trauma. Impaired renal excretion or abnormally high fluid intakes, especially as hypotonic rectal enemas, are but two other causes of this disturbance.

Numerous disorders, fulfilling the previous criteria for SIADH giving rise to water intoxication have been reported. As in the original paper by Schwartz, the syndrome is most frequently associated with non-endocrine tissue, usually an anaplastic bronchogenic carcinoma. ADH-like activity has been assayed in these cases in increased amounts in the urine, plasma and tumour tissue and has been likened, by chemical methods, to arginine vasopressin.

Frequent reports have associated the disturbance with cerebral disease of many types — T.B. meningitis, aneurysm, tumour, vascular disorders and head trauma as well as myxedema and porphyria. In these disorders it appeared that ADH-like material emanated from normal sources but was influenced by abnormal control mechanisms.

Treatment

Since all the symptoms are related to the expansion of the ECF volume, fluid restriction will irradicate them by setting off various processes acting to restore a homeostatic balance i.e. increased GFR, increased glomerular reabsorption of sodium; shift of sodium and water from the intracellular to the extracellular spaces and an eventual increase in aldosterone secretion. No other treatment will be satisfactory; a sodium load will promptly be excreted; salt retaining steroids may correct the apparent hyponatremia, but will only enhance the problem of overhydration as it is, in fact, increasing the water loading capacity. Hypertonic saline is only useful when prompt reversal of severe symptoms (i.e. convulsions or coma) is required. Here one is treating the biochemistry not the underlying disturbance. Of course, the underlying disturbance, whether it be tumor or other pathology must be definitely treated.

Importance of the Syndrome of SIADH

Hyponatremia and its accompanying symptoms may provide the first evidence of an undiscovered malignant lesion. On the other hand, this syndrome may complicate the appearance of a condition that might have otherwise been more readily identifiable. Recognition of this disorder and its irradication in terminal cancer patients will aid in preventing premature debilitation and render the last few months of life far more bearable, for severe water intoxication undoubtedly reduces the patient's ability to withstand the effects of his primary illness.

Let us hope that this short discourse will aid in the recognition, confrontation and appropriate treatment of this disorder.

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The Myth Of The Pyramidal Syndrome

"The symptom complex of a spastic paralysis without atrophy, with hyperactive tendon reflexes, absent abdominal reflexes and the sign of Babinski . . . does not result from interruption of those corticospinal fibres which arise from the precentral gyrus and pass downward through the cerebral peduncle."[3]

INTRODUCTION

For many years medical students have read and been taught that a lesion of the pyramidal tract at any level will produce the classical "pyramidal syndrome" of hyperreflexia, spastic paralysis, a Babinski response and absent abdominal reflexes, the side of the signs depending on whether the lesion is above or below the decussation of the medullary pyramids.

It is now known that a pure pyramidal tract lesion produces a picture differing significantly from this so-called "pyramidal syndrome".

Consequently, a review of the definition, structure, and function of the pyramidal tract is necessary.

DEFINITION AND STRUCTURE

Some of the difficulties that arise concerning the function of the pyramidal tract result from inaccurate concepts as to its origin and structure.

A common but erroneous view is that the pyramidal tract consists of those corticospinal fibers which arise from the giant pyramidal cells of Betz in the fifth cortical layer of the precentral gyrus. Although such fibers are present in the pyramidal tract, they actually contribute only about three percent of the pyramidal fibers.[4] Twenty-five to forty percent of pyramidal tract fibres arise from other neurons in the precentral gyrus, 30% arise from the premotor area and 40% arise from the parietal lobe.[1] As well, there may be a small contribution from the temporal and occipital cortex.[2] The pyramidal tract should thus be considered a collection of efferent fibres of widespread cortical origin which descends to the brainstem and spinal cord to modify motor activity via the gamma efferent system. The "pyramidal tract" derives its name from the fact that its fibres are the sole occupants of the medullary pyramids.[2] These descending corticospinal fibres occupy the middle three-fifths of the cerebral peduncles, and are separate and distinct from all ascending fibres, "extrapyramidal" fibres, and corticocerebellar fibres.[3] Therefore, in order to produce a lesion solely of the pyramidal tract and leave other tracts spared, either the medullary pyramids or the middle three-fifths of the basis pedunculi must be damaged. In no other regions of the central nervous system can a pure pyramidal tract lesion be produced. Lesions of the cerebral cortex, subcortical white matter, internal capsule, pons and lateral columns damage pyramidal tract fibres but more importantly, other fibres (extrapyramidal) are also damaged because of the intermingling of the various fiber bundles.

At the caudal end of the medula oblongata, 75% of the corticospinal fibres decussate to form the lateral corticospinal tract of the other side. Of the fibres that do not cross, 10% join the lateral corticospinal tract of the same side while the remaining 15% form the ipsilateral ventral corticospinal tract.[1]

FUNCTION

There is no doubt that decortication of the precentral gyrus, a capsular lesion, or a lesion of the lateral columns of the spinal cord produces severe motor deficits in man or animal. The classical "pyramidal syndrome" is often seen as a consequence of such lesions. However, as explained above, such lesions also affect bundles other than the definitive pyramidal tract and it is the purpose of this article to show that it is the damage to those "extrapyramidal" fibres that results in the classical "pyramidal syndrome".

In 1940, Tower showed that section of the medullary pyramid in a monkey resulted in an immediate contralateral hemiparesis without hyperreflexia.[7] Subsequent investigation confirmed these results and it was observed that some time after complete section of the medullary pyramid or cerebral peduncle, the animals exhibited contralateral hypotonia and slight hyperreflexia. Immediate limb paresis was followed by excellent return of function of the involved limbs if the animals were observed long enough and encouraged to use their paretic limbs. Bercy et al[1] found that following cerebral pedunculectomy, monkeys eventually regained excellent use of the involved limbs although the limbs remained hypotonic and hyporeflexic. Animals with extensive lesions of the cerebral peduncles could walk, run, and pick up food.

In 1964, Bucy et al[2] reported the case of a man who underwent a right cerebral pedunculotomy for the relief of a left hemiballismus. Except for the abnormal movements, neurological examination prior to operation was normal. The central portion of the right cerebral peduncle was divided. Following operation, the hemiballistic movements were abolished and the patient exhibited a complete left hemiparesis. Within 24 hours after operation he began to voluntarily move his left arm and leg. Upon full recovery he exhibited an incomplete left Babinski response and minimally weak left extremities which were slightly hyperreflexic but with normal tone. Voluntarily fine, well co-ordinated movements of all limbs were well performed although he was slightly clumsier when using his left arm and leg. The patient died two and a half years after his operation of unrelated causes and post-mortem examination confirmed the accuracy and completeness of the pyramidal tract

lesion. Some of the excellent motor facility of hand and leg which this man regained can possibly be attributed to intact innervation from the ipsilateral cerebral cortex via the ventral corticospinal tract. However, the fact that a hemidecortication or a unilateral capsular lesion produces a gross contralateral motor deficit while a cerebral pedunculotomy does not, implies that the involved extremities are receiving motor innervation via pathways other than the definitive tract.[2]

Bucy states that "the pyramidal tract is not essential to the useful control of the skeletal musculature. Furthermore, in the absence of the corticospinal fibers, other fiber systems possibly passing through the mesencephalic tegmentum are capable of producing well co-ordinated movements of the extremities."[4] These "other fiber systems" have been designated the "extrapyramidal motor system" and it is now known that simultaneous involvement of this system is responsible for the spastic paralysis and hyperreflexia seen when lesions occur in the cortex, internal capsule, or lateral columns of the spinal cord. It may be that the purpose of the pyramidal tract is to convert clumsy, unskilled movements into fine, well controlled movements.[4]

Pure pyramidal tract lesions will produce a "partial Babinski sign"; that is, the great toe will extend on plantar stimulation, but the other toes will not fan. Fanning occurs with a lesion of the extrapyramidal tract. To exhibit these signs, the portion of the pyramidal and extrapyramidal tracts supplying the foot must be involved by the lesion and the peripheral neuroskeletomuscular mechanisms must be intact.[3]

SUMMARY

The fact that the classical "pyramidal syndrome" does not occur with pure pyramidal tract lesion has been shown by several eminent investigators. Bucy suggested that the terms "pyramidal" and "extrapyramidal" be discarded in favor of a new integrated concept of the neural control of muscular tone and movement.[3] While we must pay heed to recent advances in any field and try to relate them to the classical picture of the living patient, the concept of the pyramidal syndrome can still be valid if we realize that the resulting neurological signs are in fact due to involvement of both pyramidal and extrapyramidal motor fibers.

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Clinicopathological Conference

Long Term Complication Of Recurrent Steatorrhea

CASE PRESENTATION

A 37-year-old male was seen in April 1967, complaining of a dry non-productive cough, persisting low grade fever, marked shortness of breath, profuse night sweats, periodic chills and a weight loss of approximately 15 pounds over a four-month period.

In March 1954, the diagnosis of pulmonary tuberculosis was made while the patient was in England and he was treated with triple antituberculous therapy and subsequently a right upper lobectomy.

In 1956, while in New Zealand, he was investigated for diarrhea, weight loss and easy fatigability. The diarrhea was described as bulky, frothy, with 5 - 10 loose stools per day. He lost 35 lbs. in weight and was noted to have a stomatitis, abdominal distention, slight clubbing of the fingers and hypotension. Laboratory investigation revealed a macrocytic anemia with a megaloblastic marrow, which failed to respond to iron and folic acid but did response to Vitamin B12. Hypoproteinemia with a total serum protein of 4.6 gm%, serum albumin of 1.9 gm% and serum globulin of 2.7 gm% was noted. A flat glucose tolerance test curve was also found. Small bowel series showed distention, segmentation and flocculation, consistent with a malabsorption syndrome. Stool cultures and examination for ova and parasites were negative. Fecal fat balance revealed 60% fat absorption. He was treated with a high calorie, low fat diet, vitamin B12 and multivitamin supplements and responded well.

The patient did well until 1958, when he had a relapse. He was treated with a gluten-free diet; diarrhea was controlled and he regained weight.

For the following 5 years the patient continued free of symptoms despite non-adherence to his prescribed diet. However in 1965, during a tour of naval duty in the South China Sea, the patient noticed the recurrence of diarrhea and subsequent weight loss of approximately 20 lbs. Throughout the latter part of 1965 he experienced a marked change in bowel habits with one to two frothy, bulky, offensive movements per day, often containing undigested food matter.

In January 1966, the patient moved to Canada and noted continuing diarrhea, loss of weight, a decrease in his sense of well-being, increased fatigability and lethargy.

In April of 1966 routine chest films showed calcification in both hilar areas but no active parenchymal disease, however subsequent sputum examinations were positive for acid-fast bacilli. He was started on PAS and streptomycin.

He was aware of abdominal distention and noted increased flatulence. He denied any bruising tendency, paresthesia, bone pain but did note some dryness of the skin. Physical examination revealed a somewhat pale, underweight, prematurely grey, asthenic male. Positive findings were few and consisted of a right thoracotomy scar, dryness of the skin and slight abdominal distention.

Laboratory studies revealed: — Hbg. 14.7 gm%, WBC 4500, smear and differential were normal. ESR-27 mm/hr. Prothrombin time 18 seconds. Serum carotene 0 micrograms %. Total protein 6.9 gm%, albumin 4.3 gm%. Serum cholesterol 111 mg%, serum calcium 8.8 mg%, serum phosphorus 3.1 mg%. Schilling test revealed 0% urinary output of the administered dose. The 24 hour fecal fat excretion was 58.3 gm/24 hrs. Urine xylose was 1.5 gm/5 hrs. Stools were negative for ova and parasites. Stool cultures were normal.

Small bowel series was compatible with a malabsorption syndrome. A small bowel biopsy was consistent with adult celiac disease.

The patient was started on a gluten-free, low-fat diet, vitamin replacement therapy and his symptoms improved. Over a three-month period he regained 20 lbs. in weight. Repeat chest X-rays showed no active parenchymal disease and sputum examinations were persistently negative for tubercle bacilli.

The patient did well until April 1967 when he presented with a dry non-productive cough, fever, chills and posterior cervical lymphadenopathy.

Remarkable laboratory studies revealed an ESR of 36 mm/hr. and an eosinophilia on peripheral blood smear. Repeated sputum examinations were negative for acid-fast bacilli and sputum cultures failed to grow tubercle bacilli.

On April 27th, the patient was taken to the operating room and an abdominal mass was removed for biopsy. It proved to be a lymph node, whitish grey in colour, rubbery in consistency and irregular in outline. A repeat small bowel biopsy was consistent with severe adult celiac disease. Chest X-rays showed an increased density most marked in the left hilar region. Small bowel films suggested an intrinsic polypoid mass in the upper jejunum with some narrowing of the bowel below this area.

While in hospital, the patient continued on a gluten-free diet but despite therapy his condition deteriorated rapidly, with increasing shortness of breath and weight loss. Generalized lymphadenopathy developed involving the cervical, axillary and inguinal areas. No hepatosplenomegaly was noted. The prognosis was felt to be ex-

tremely poor and the patient was advised to return home to New Zealand.

He died in hospital on August 11th, 1967.

DISCUSSION OF DIFFERENTIAL DIAGNOSIS BY DR. E. J. PROKIPCHUK

In summary, we are dealing with a 37-year-old male who developed pulmonary tuberculosis which responded to antituberculous therapy and a right upper lobectomy in 1954. However in 1966, following an exacerbation of a co-existing gastrointestinal disease with recurrence of malabsorption syndrome, reactivation of pulmonary tuberculosis occurred. This was not evident radiologically but several sputum examinations were positive for acid-fast bacilli.

In 1956 the patient developed symptoms, signs and laboratory findings consistent with a malabsorption syndrome. A relapse occurred in 1958, which responded to a gluten-free diet. Despite the patient's not adhering to this diet for 5 years, he did quite well until another recurrence occurred in 1965. Subsequent investigation in 1966, confirmed the diagnosis of a malabsorption syndrome of a profound degree with a fecal fat excretion of 58.3 gm per day. A small bowel biopsy was consistent with adult celiac disease and he responded well to a gluten-free diet, and vitamin replacement therapy.

The differential diagnosis of malabsorption syndrome will be discussed only briefly since the diagnosis was well established in this case. Malabsorption syndrome may be divided into 2 large groups, (a) *digestive disorders* as seen in disorders of exocrine secretion such as pancreatic and hepatobiliary disease as well as alteration in gastroduodenal integrity with resultant poor and inadequate admixture of food and exocrine secretion and (b) *Absorptive disorders* which include mucosal derangement as seen in adult celiac disease (gluten-induced enteropathy, non-tropical sprue), tropical sprue, infiltrative lesions of small bowel (eg. Whipple's disease, amyloid, scleroderma and reticuloses) and agents causing mucosal damage such as parasitic infestations, inflammatory disease of small bowel, radiation enteritis or drugs (eg. folic acid antagonists, anti-mitotic drugs, neomycin, etc.). Loss of absorptive surface due to extensive small bowel resection also causes malabsorption. Lymphatic obstruction as in intestinal lymphangiectasia or vascular disease as superior mesenteric occlusion or polyarteritis cause absorptive defects. Blind loop syndrome, intestinal strictures, jejunal diverticulosis and entero-enteric fistulas etc. allow bacterial overgrowth and competitive absorption of vitamin B12 by the bacteria. Bacterial overgrowth may also cause deconjugation of bile acids and therefore impaired intraluminal lipolysis. The list of malabsorption syndromes is lengthy and the above are included as a partial list.

In this patient, the diagnosis of adult celiac disease was well established. His disease was noted at age 27 in New Zealand and in 1958 he responded well to a gluten-free diet. The clinical pictures and response to a gluten-free diet as well as the small bowel biopsy findings with villous atrophy would be consistent with the diagnosis of adult celiac disease. The patient had not travelled to the tropics or subtropics and the absence of hematological response to folic acid, but a good response to vitamin B12 would mitigate against tropical sprue. In tropical sprue folic acid usually corrects the anemia and the intestinal lesion although treatment may be required for several months. At times folic acid alone is not sufficient and broad-spectrum antibiotics in combination with folic acid will be effective.

Intestinal tuberculosis may be considered briefly only to be discarded. Tuberculosis involves primarily the terminal ileum and cecum, but may occasionally involve more extensive areas of the small bowel. This patient had received adequate antituberculosis therapy and was considered an abacillary case of pulmonary tuberculosis when he developed a malabsorption syndrome. There was no radiological evidence of ileal stricture or localized disease of the ileum and cecum. The radiological picture in this patient was that of a diffuse disease of the small bowel.

There was no evidence radiologically of Crohn's disease, ileojejunitis and we may discard scleroderma, in view of the lack of peripheral involvement. Whipple's disease may be partially excluded due to the arthritis which occurs in about 60% of cases, but was definitely excluded following the small bowel biopsy, which failed to show the characteristic lesion of PAS-positive macrophages in diluted villi.

The patient did well following his investigations in August of 1966 for approximately 7 months, when he presented with a dry non-productive cough, low grade fever, shortness of breath, posterior cervical lymphadenopathy and subsequently generalized lymphadenopathy as well as possible intramural jejunal mass. No hepatosplenomegaly was initially noted. Repeated sputum examinations and cultures were negative for tubercle bacilli.

The clinical picture suggested a possible re-activation of tuberculosis, but repeated sputum examinations were negative and the chest X-ray showed no active parenchymal disease.

With the findings of posterior cervical and left hilar lymphadenopathy and subsequent generalized lymph-node enlargement with a low grade fever, a neoplastic lymphoproliferative process would have to be considered. The association of malignant lymphoma and adult celiac disease is now well-established. Since Gough et al first drew attention to this relationship in 1962, several other groups have reported series of patients with adult celiac disease with subsequent development of malignant lymphoma occurring years after the diagnosis of celiac disease was made. Characteristically, the celiac patient in

whom lymphoma is most likely to occur is a male over the age of 40, in whom the disease has been present for more than 10 years and who has not been on a gluten-free diet. The presence of a lymphoma should be suspected when new symptoms such as abdominal pain, weight loss, fever, diarrhea and lymphadenopathy occur. In celiac disease the sedimentation rate is usually normal or slightly elevated and the serum globulin level is low or normal. If one sees an elevated ESR or a high or rising serum globulin level it should raise suspicion of the development of a lymphoma. Reticulum cell sarcoma is the commonest lymphoma seen in adult celiac disease and therefore the final diagnosis in this case would be:

1. Malignant lymphoma — probably reticulum cell sarcoma.
2. Adult celiac disease.
3. Pulmonary tuberculosis — abacillary, inactive.

POST MORTEM FINDINGS

GROSS

The body was that of an extremely emaciated young male.

Both pleural cavities contained several hundred millilitres of straw-coloured fluid. The trachea and bronchi contained frothy mucous. The pulmonary hilar nodes were confluent with solid white peribronchial tumour extending around the root of both lungs. Tumour filled the subpleural lymphatics.

The small and large bowel were grossly not remarkable. No obvious tumour, ulceration or mucosal atrophy could be demonstrated. The liver was grossly enlarged and diffusely infiltrated with greyish tumour throughout.

The spleen weighed 1358 gm and was grossly enlarged and firm. There was gross enlargement of lymph nodes in all groups. The nodes were hard, white and homogeneous on section. There was nodular enlargement of all pharyngeal lymphoid tissue and the posterior one quarter of the tongue was thickened by white submucosal tumour.

MICROSCOPIC

The microscopic examination of lymph nodes, pharynx, spleen and liver showed diffuse infiltration and replacement of normal structure by actively proliferating anaplastic cells of the reticulum cell sarcoma type.

In the jejunum the mucosa showed the villi to be very irregular and variable in size and shape. Many were thick, short and fusion was evident in several places. In the ileum, colon and rectum, diffuse and focal mucosal and submucosal infiltration with reticular cell sarcoma was found. In some areas these had expanded into nodules and quite extensive plaques.

The lungs showed solid sheets of reticulum cell sarcoma surrounding and eroding all normal tissue.

PATHOLOGICAL DIAGNOSIS

1. Generalized reticulum cell sarcoma.
2. Adult Celiac Disease.

DISCUSSION

Steatorrhea occurring with malignant lymphoma of the small intestine has been recognized for more than twenty-five years. Prior to 1950 the steatorrhea was considered to be the result of either mesenteric lymphomatous lymphadenopathy (with lymphatic block) or diffuse lymphomatous infiltration of the small bowel, and at that time the malignant lymphoma was considered to be the primary disease. This concept was challenged by Gough et al, who in 1962 described three patients with adult celiac disease (ACD) that subsequently developed reticulum cell sarcoma. He proposed that the small bowel reticulosis developed as a consequence of the ACD which was the primary disease entity. This argument has been supported by several other workers, including Austad et al who fully reviewed the subject in 1967, and it is well documented at the present time that malignant lymphoma of the small bowel may develop as a complication of ideopathic steatorrhea (IS) or ACD.

In these cases, ACD or IS is well established clinically in the patient several years before the onset of the secondary lymphoma of the small intestine. The patient usually has a long-standing history of loose, pale stools associated with weight loss and wasting. Glossitis, atrophic tongue, and angular stomatitis are not infrequent findings. On laboratory investigation these patients have an elevated ESR; a megaloblastic anemia with a flat glucose tolerance curve; a typical malabsorption pattern on roentgenograms of the small bowel; and a positive peroral biopsy of the small bowel mucosa which gives a definitive diagnosis. The patients respond well to a gluten-free diet. Gough emphasizes the length of the history, the flat glucose tolerance curve, macrocytic anemia, and a clinical response to a gluten-free diet as being the most significant findings to establish ACD or IS as the primary lesion.

The diagnosis of a malignant lymphoma of the small bowel as a complication in patients with ACD or IS can be made on clinical grounds. There is a general decline in health with a failure to respond to low fat, gluten-free diet which had previously held the patient in complete remission. The patient again has diarrhea with weight loss and lassitude for no apparent reason. The ESR rises and there is a persistent low grade fever. The patient complains of central, colicky, abdominal pain and in some cases a tumour mass is palpable which rarely could lead to signs of subacute bowel obstruction or perforation. A dry, scaly, itchy skin rash may appear. When this clinical picture presents in a patient known to have ACD or IS (usually about 15 - 20 years after diagnosis) lymphoma of the small bowel should be suspected and early laparotomy is indicated.

Reticulum cell sarcoma is the commonest form of malignant lymphoma that presents as a complication of ACD or IS. These tumours usually are pleomorphic, consisting of round, oval, or spindle cells showing nuclear hyperchromatism, nuclear pleomorphism, mitosis and occasionally multinucleated cells. The reticulin pattern is usually fibrillary and is well developed in spindle areas. These tumours, in most cases, have metastasized either to the abdominal glands or beyond to widely disseminated deposits by the time they become apparent clinically. The incidence of malignant lymphoma of the small bowel complicating ACD or IS is not well known but the latest published figures quote about 7% with a sex ratio of 9/5, being more common in the male sex. The mean duration of years in which symptoms of ACD or IS antedate the lymphoma is approximately 21 years and malignant change usually occurs between the ages of 48 - 57 years. The mean duration of new symptoms that led to the diagnosis of a lymphoma is 0.4 years. It should be pointed out here that ACD and IS predispose to other malignant changes in the body, especially carcinoma along the gastro-intestinal tract.

To confirm that the lymphoma is secondary to ACD or IS one must establish a definite diagnosis (with biopsy) of ACD or IS many years before the onset of the lymphoma. If the two diseases present clinically within a short time of each other no definite conclusion can be reached as to which is the primary lesion. It is known that only 20% of patients with lymphosarcoma or reticulum cell sarcoma live for two years or more; therefore, it seems unlikely that such a highly malignant lesion could cause ACD or IS which manifests itself clinically for some 21 years. The obvious question to follow then is how does ACD or IS predispose to malignant lymphoma of the small bowel?

The pathogenesis of this condition is merely theoretical. In the normal small bowel, epithelial cells ascend from the crypts to the tips of the villi before being discarded. In celiac disease this process is disturbed with a lack of differentiation of the epithelial cells which appear to be produced at a greater speed than normal. There is a disruption of the basement membrane and infiltration with plasma cells and lymphocytes. There is a lymphoid hyperplasia in the intestinal mucosa. It has been shown that the severity of the mucosal disturbance increases as one moves proximally which correlates well with the decreased incidence of lymphoma of the distal bowel. Can this lymphoid hyperplasia lead to a malignant lymphoma in the small bowel? Austad et al, proponents of this theory, maintain that this is the actual mechanism involved in the malignant change. Other theories have been postulated — the abnormal mucosa is itself precancerous; the abnormal epithelium is more easily penetrated by carcinogens or viruses; chronic inflammation in the lamina propria is associated with lymphoid hyperactivity that predisposes patients to lymphomatous complications (after Austad); or environmental factors (such as diet, intestinal organisms) may account for this predilection to lymphoma. It has been suggested that celiac disease may be due to a disorder of the immunological mechanism, for example — the production of abnormal antibodies; lymphoreticular insufficiency; and disorders of serum globulins. Workers have attempted to associate this theory with the fact that an impaired immune response is seen in association with some cases of carcinoma. There is a great deal to learn about the pathogenesis of this disorder; however, it is hoped that research in the field of immunology may solve some unanswered questions.

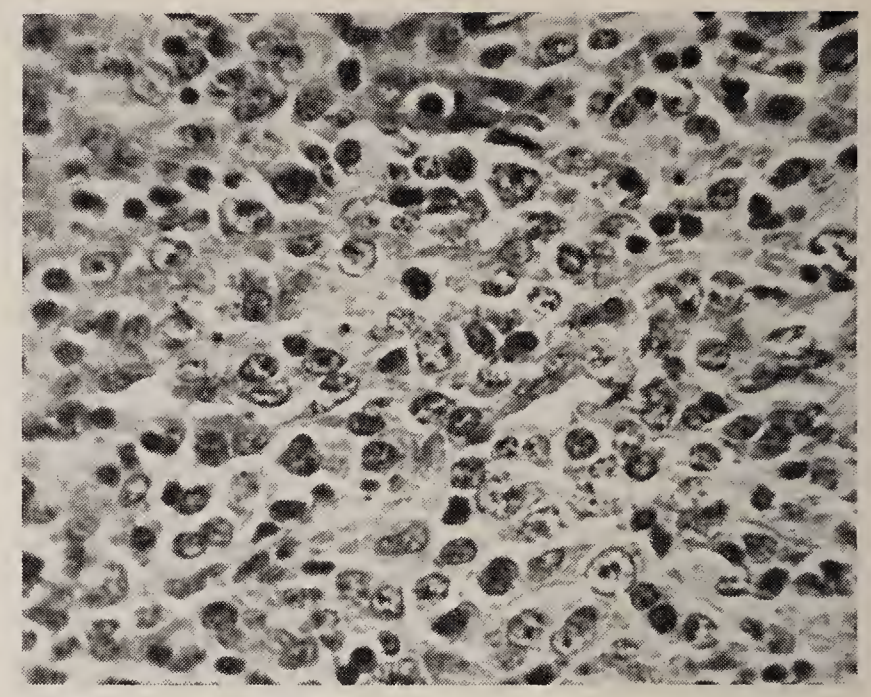

FIG. 1. The cervical lymph node shows a massive infiltration by pleomorphic cells with prominent, irregular nuclei that is consistent with a diagnosis of reticulum cell sarcoma.

In summary, a case of malignant lymphoma as a complication of long-standing adult celiac disease was presented. The clinical presentation, pathology, and theories regarding pathogenesis were discussed briefly from a review of the literature.

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ACKNOWLEDGEMENT

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Assaeries Miscellaneous Abstracts - Some Blebs From The Literature

MEDICAL STUDENT PERSONALITY — I.Q. STUDIES

The studies on medical student I.Q. by Rutherford and Coles (referred to in Vol. XLVI, No. 1, Nov. 1968 of this journal) have now been published. They have elaborated several interesting facets of the problem of the "I.Q. Shift". Although the average medical student's I.Q. drops 18.3 points from first year to fourth, the authors have shown that the most drastic changes take place in students with the highest I.Q. Students with lower I.Q. initially (less than 118) showed considerably smaller shifts (an average of 7.2 points decline), and several students with particularly low intelligence quotients even showed a rise over the four years of professional training. It was felt by the authors that these new findings will be extremely encouraging to a great number of medical students.

MEDICO-LEGAL CASE

A case has been reported recently in which an eighty-five year old female patient has sued the University following an incident in which a staff gynecologist, along with twenty-five of his third year medical students, performed vaginal examinations upon her for forty-five minutes continuously. She has claimed these examinations were performed in rapid succession, occasionally two or three at a time. The outcome of the suit will rest heavily on the evidence of the Royal Canadian Mounted Police who at present are dusting her cervix for fingerprints.

FOURTEEN THOUSAND KIDNEYS MEASURED

In a series of seven thousand outpatients at the Boston Walking-Through Hospital, Gimpel and Mason have recently shown several unrecognized anatomical variants in the general population. Of special note is their discovery that low kidneys are found almost exclusively in short people.

A STEP IN THE DIRECTION OF STUDENT SELF-DETERMINATION

A bulletin recently issued by the Curriculum and Examinations Committee of the Faculty of Medicine of Yorstruly University indicates clearly that its recent enlightened education policy ranks it among the most advanced medical schools on the continent. For many years now, in keeping with current educational theory, the Faculty has made attendance at lectures and laboratories non-compulsory. In a gesture that it feels will thoroughly modernize medical education, the Faculty now has announced that writing the final examinations will also no longer be compulsory. Attendance will be left to the discretion of the individual student; however, the Committee pointed out that it was to the student's advantage to write his examinations, since otherwise he would be required to repeat his year.

THE CLERKSHIP

The University of Toronto has announced that it will not graduate a class in medicine for the present year. Following the introduction of its seven week lecture program in the final year it has lost seventeen students to the study of languages, thirty-eight more to political science and philosophy, and twenty-four to drama and instrumental music. Of the remainder of the graduating class, five students are now training as fishing guides and the rest of the group are sailing to the Fiji islands on a balsa wood raft.

A. J. Shoichet

THE WEBSTER PRIZE

The editors are pleased to announce that Arnold J. Shoichet has been awarded the WEBSTER PRIZE for 1968-69. The award was made in recognition of the originality and literary acumen which he displayed in the articles written in the feature known as Assaeries.

Each year all student writers are eligible for the award. Selection of the best article is made by the Academy of Medicine and the prize of fifty dollars, endowed by Mrs. Annie Webster in memory of Dr. J. D. Webster, is awarded annually at the Academy of Medicine Library and Historical night.

We wish to thank the Academy of Medicine for their recognition, encouragement and promotion of student journalism.

Eponyms And The Men

NIELS STENSEN (1638 - 1686) or "Nicholas Steno" was born in Copenhagen, Denmark and raised by his grandparents. His later linguistic talents were amply demonstrated by his anatomical, mathematical, and geological papers in Hebrew, Greek, Latin, French, German, Dutch, Italian and English. Leaving the University of Copenhagen after three years, Stenson studied anatomy at Amsterdam under a Professor Blasius, with whom he later quarreled over rightful ownership of the discovery of the parotid duct which now bears Stensen's name. Although he originally showed the presence of this duct in a sheep, it was the Frenchman François de la Boe Sylvius (of neuroanatomical fame) who later demonstrated it in man. Stensen proceeded to investigate the glands of the eye and later the musculature, on which he wrote his important 1664 work (dedicated to King Friedrich III of Denmark) "On the Muscular Nature of the Heart." It was one of the great anatomic discoveries of his era. The years 1665 to 1667 saw Stensen a travelling lecturer in France and Italy where he was converted from Lutheranism to Roman Catholicism. His conversion was ultimately responsible for his retirement from medicine in 1674 and his subsequent exclusive devotion to the work of the church. In 1675 he was ordained a priest and in 1677 consecrated Bishop of Titiopolis. Pope Innocent XI allowed him to leave Italy as "Apostolic Vicar for the Northern Missions" in Germany where he died in 1686. He is buried in the Basilica of Saint Lawrence in Florence.

One of the greatest, albeit unforeseen, contributions to medicine by a non-medical person was the discovery and implementation of Roentgen- or X-irradiation by WILHELM CONRAD ROENTGEN (1845 - 1923), the German physicist. An example of a widely travelled man, his education took place in the Netherlands, Zurich, and Wurzburg. His professorship in mathematics and physics began as a *Privatdocent* (unpaid lecturer) at Strasbourg in 1874; sessions at Hohenheim (1875), Giessen (1879), Wurzburg (1885), and Munich (1900) followed. At Wurzburg in 1895, Roentgen discovered the new irradiation which he first thought to be longitudinal vibrations in the ether and not transverse as those of light. In deference to his uncertainty regarding their nature, he designated them X-rays. The Rumford Medal of the Royal Society (1896) and the Nobel Prize (1901) reflected the impact of his discovery upon the scientific community. Roentgen remained a prolific researcher of diverse interests, including elasticity, capillarity, piezoelectricity, and the electromagnetic rotation of polarized light.

JEAN-MARTIN CHARCOT (1825 - 1893) was the son of a Parisian coach-builder of limited means. Legend has it that his father sent his three sons to school for a year. Whoever did best could go on to higher education, the middle son would be trained for the army, and the son who did poorest would follow in his father's steps. Jean-Martin came first and subsequently graduated in medicine. While interning at the Salpêtrière, he wrote a thesis in which he distinguished between gout and rheumatoid arthritis for the first time. Continuing there for the remainder of his life, he became in 1882 the world's first Professor of Neuropathology. He achieved world fame in his day largely because of the splendid lectures and demonstrations which he devised. He was one of the first to hold theatre clinics and he began the fashion, so well continued by modern neurologists, of imitating any disturbance from a minor nerve palsy to grand mal epilepsy. He wrote prolifically; in his papers can be found original descriptions of intermittent claudication, disseminated sclerosis, amyotrophic lateral sclerosis, and neuropathic joint disease. His "arthropathy of ataxic patients" became known as a *Charcot joint*.

LUDWIG ASCHOFF (1866 - 1942), the son of a distinguished physician, rose through the ranks of German pathologists to become Director of the Pathological and Anatomical Institute in Freiburg im Breisgau. The literature has been greatly enriched by Aschoff's many original contributions, including those on the effects of Staphylococcus pyogenes on inflamed tissues, on Ehrlich's side-chain theory and its application to artificial immunization, on the process of arteriosclerosis, and on the conduction system of the mammalian heart in health and disease. Aschoff's institute soon became an international research centre. Among his students were many Japanese, and the various articles which he co-authored with them led to his great influence over Japanese pathology and medicine. In later years he published original works concerning the origin of monocytes, the formation of gallstones, goitre, the pathochemistry of bilirubin, the course of tuberculosis, the pathology of the stomach, bacterial flora of the normal and inflamed appendix, and thrombosis. The conception of general pathology and its correlation with physiology and clinical medicine is best illustrated in Aschoff's "Textbook of Pathologic Anatomy." During the late nineteen thirties and early forties, he was justly looked upon as the greatest living pathologist, who was to be not only eponymously associated with the classic rheumatic nodule but also recognized as one of the most impressive personalities in the history of medicine.

Gordon D. Hardacre, B.Sc. 7T0

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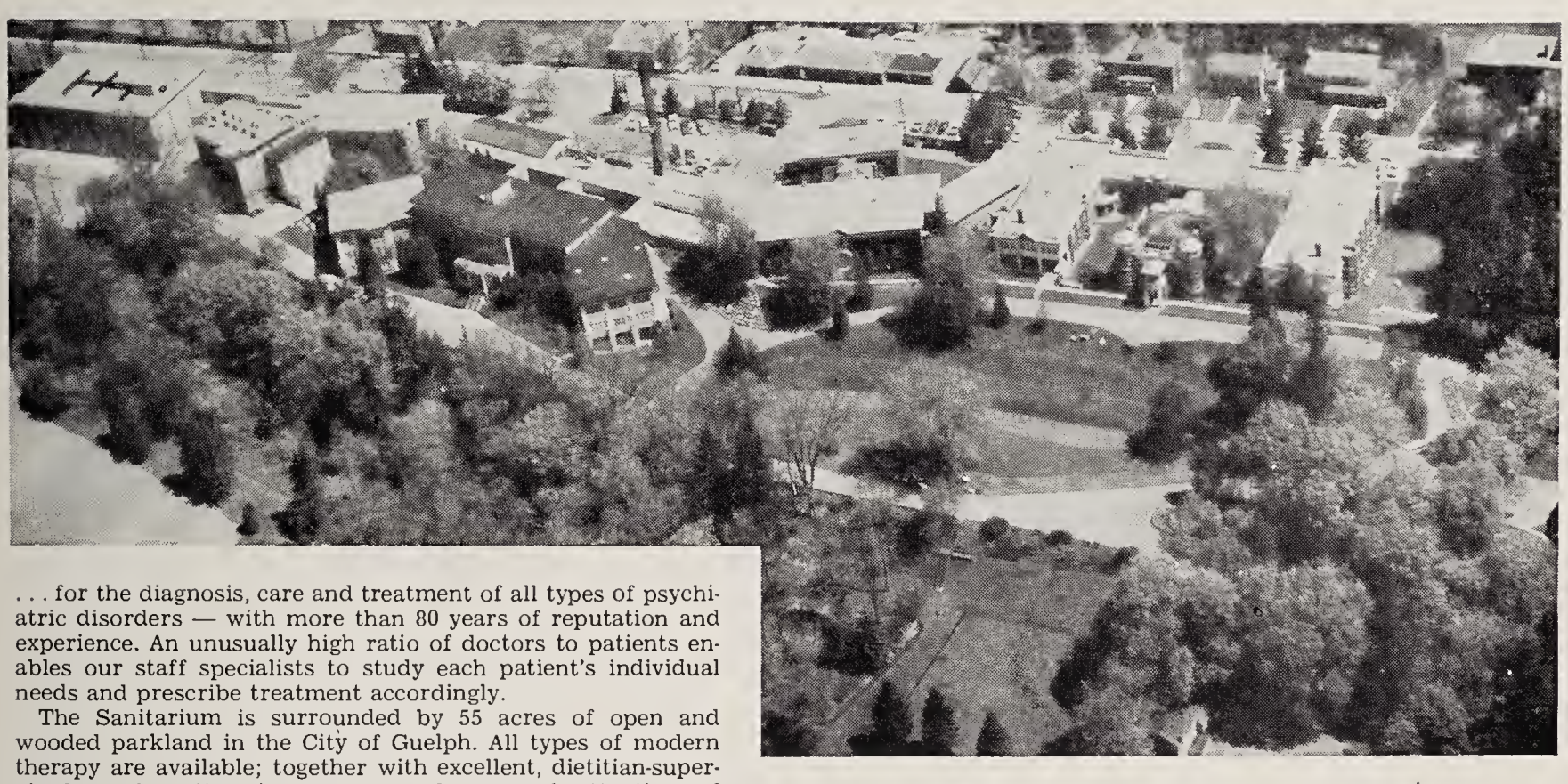

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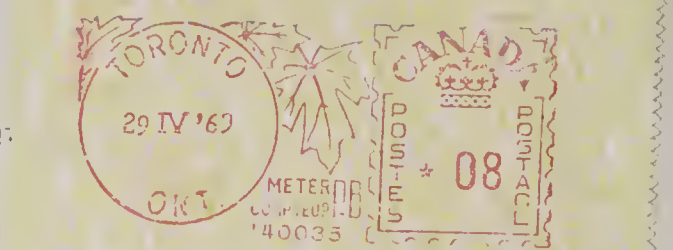

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